STUDY OF AUTONOMIC NERVOUS SYSTEM DYSFUNCTION IN

PARKINSON'S PATIENTS

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CERTIFICATE

This is to certify that this Dissertation entitled,

"STUDY OF AUTONOMIC NERVOUS SYSTEM DYSFUNCTION IN PARKINSON'S PATIENTS" is a bonafide record of work done by **Dr.E.ARUN RAJ** under our guidance and supervision in the Institute of Neurology, Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai, submitted as partial fulfillment for the requirements of D.M. Degree examination Branch I NEUROLOGY, AUGUST 2013, under the Tamil Nadu Dr. M.G.R. Medical University, Chennai.

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CONTENTS

INTRODUCTION

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Parkinson's disease (PD)[1] is a chronic neurodegenerative progressive neurological disease with clinical features viz rigidity, bradykinesia, rest tremor and postural instability. Assymetry is a prominent feature of this disease. PD ranks second among the common neurodegenerative disease next only to Alzheimer's dementia.

The pathological characteristic of PD is intraneuronal alpha synuclein positive Lewy bodies and loss of neuronal cell. Apart from classical motor symptoms PD patients also develop non motor symptoms. Non motor symptoms cause a major disability in PD and the prominently contribute to decreasing quality of life especially in advanced stages of disease. The major non motor symptoms are olfactory loss, psychiatric disturbances of depression and anxiety, sleep disorders, cognitive dysfunction, and chiefly the Autonomic Dysfunction.

Autonomic symptoms in Parkinson's disease (PD) were first reported in 1817 by James Parkinson himself. He described abnormalities of salivation and sweating, and dysfunction of the alimentary tract and urinary bladder. Patients rarely volunteer symptoms of autonomic disturbance in clinic, and perhaps because of this, there has been little interest in autonomic dysfunction in PD until recent years. Demonstration of the importance of

dysautonomia in Parkinsonism patients, led to a recent resurgence in this area. The introduction of standardised diagnostic criteria for PD has improved diagnostic accuracy, and reports since the introduction of these guidelines continue to suggest that between 50% and 80% of subjects have objective evidence of autonomic involvement

Autonomic nervous system disturbances are seen in advanced PD but are not as early or severe as in Multiple System Atrophy[1,17,19]. Dysphagia may be prominent in some patients with severe PD when it is usually accompanied by marked dysarthria. Some patients develop urinary frequency and urgency by day as well as nocturia. Postural hypotension[1] is the most common manifestation but it may be difficult to assess the relative contributions of the disease and medications, especially dopamine agonists. The fall in blood pressure is severe or disabling in idiopathic Parkinson's disease. Impotence is frequently reported and is probably secondary to autonomic involvement, depression, and physical immobility, especially at night. Constipation[1] is very common in Parkinson's disease at most stages of the condition and is sometimes severe, requiring hospital admission. Though there are several factors underlying this like reduced exercise, dietary changes, and the effects of anticholinergic drugs, dysautonomia chiefly contribute to the cause. Many patients notice

increased sweating; in the later stages of the condition, especially in severe off periods in levodopa treated patients, there may attacks of drenching sweating with immobility, fear, and often pain. Thus autonomic symptoms include reduced gastrointestinal tract motility with postprandial bloating, constipation, urinary problems, sexual problems, disordered sweating, and orthostatic hypotension. The advances in management of this autonomic symptoms stresses the need for identification of autonomic symptoms early and improve the quality of life.

Hence we have undertaken this study to assess the autonomic dysfunction in PD, their prevalence, early identification and clinical testing, so as to diagnose early autonomic dysfunction, in order that suitable treatment may be initiated to improve quality of life.

AIM OF THE STUDY

AIMS OF THE STUDY

The main aims of the study

1. To evaluate the prevalence of autonomic nervous system dysfunction in Parkinsons's disease
2. To assess the prevalence and the impact Of Age, Sex, Duration of PD on severity of Autonomic Dysfunction
3. To Assess The Correlation Of Hoehn And Yahr Staging of Parkinson's Disease And Autonomic Dysfunction
4. To correlate the prevalence of Cardiovascular Autonomic Nervous System dysfunction in PD patients based on basic cardiovascular autonomic function tests with that of staging.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Autonomic nervous system(ANS) is broadly classified into sympathetic and parasympathetic system[1]. The sympathetic system is also known as thoracolumbar "outflow", because the neurons start in the thoracolumbar (T1-L2) regions of the spinal cord[1]. The parasympathetic system is also known as "craniosacral outflow", because the neurons start mainly from the cranial nerves (CN III, CN VII, CN IX, CN X) and sacral (S2,S3,S4) segments of spinal cord. There is a third system called enteric nervous system.

The ANS is has two sets of neuron viz preganglionic neuron that initially synapse with the postganglionic neuron and then synapsing with target organ.

Sympathetic system

The sympathetic nervous system (thoracolumbar outflow)[1] preganglionic fibres arise from cells located in the (intermediolateral cell columns from T1 to L2 segments of spinal cord. The preganglionic neurons synapse for their postganglionic neurons at the following locations.

Paravertebral ganglia belonging to the sympathetic chain are present on both sides of the vertebra.

Prevertebral ganglia consisting of celiac ganglion, aorticorenal ganglion, superior and inferior mesenteric ganglion, aorticorenal ganglion.

Adrenal medulla Chromaffin cells synapse directly onto the target cell.

Parasympathetic system[1]

Craniosacral outflow[1] arise from the following two regions:

1. Cranial Nerves III, VII, IX, X
2. Sacral segments of spinal cord S2, S3, S4.

In the sympathetic system, the preganglionic fibres are relatively short, myelinated and cholinergic whereas the postganglionic fibres are long. unmyelinated, primarily adrenergic with the exception of cholinergic sweat glands. In the parasympathetic system the preganglionic fibres are long and postganglionic fibres are short and cholinergic. These two systems modulates vital functions, in antagonistic way only to maintain homeostasis. Following are actions of the sympathetic and the parasympathetic system

Sympathetic nervous system

- Diversion of blood flow to vital organs and restriction of flow to gastrointestinal system and skin by and restriction of flow to by vasoconstriction.
- Blood flow to skeletal muscles and the lungs are enhanced
- Bronchodilation
- Increases heart rate and blood pressure and the contractility of heart cells
- Pupillary dilation and relaxation of the ciliary muscle to the lens which allows entry of more light to eye and farther vision.
- Coronary Vasodilation.
- Constriction of both intestinal and urinary sphincter.
- Inhibition of peristaltic movement and thus bowel motility
- Stimulates orgasm and ejaculation

Parasympathetic nervous system

- Dilatation of blood vessels of the gastrointestinal tract.
- Bronchoconstricrion
- Decrease heart rate and blood pressure

- During accommodation, constriction of the pupil and also contraction of the ciliary muscle to the lens, helping in closer vision.
- Stimulates salivation, and
- Accelerates peristalsis, so, mediates digestion of food, GIT motility and indirectly, the absorption of nutrients.
- Genital erection , through the pelvic splanchnic nerves S2–4.

Parkinson's diseae

Clinically, Parkinson's disease may be defined[8] as,

- the presence of two out of the three cardinal features of bradykinesia, rigidity, and tremor; postural instability tends to occur later;
- a good clinical response to levodopa; and
- no 'atypical' features suggestive of another Parkinsonian syndrome.

Pathologically there is extensive loss of pigmented dopaminergic substantia nigra neurones and the presence of Lewy bodies[8,37,38,39].

Epidemiology[8]

Numerous studies have yielded crude prevalence rates of 10-400 cases per 1,00,000 people (Zhang and Roman 1993)[12]. These estimates are difficult to compare due to different ascertainment methods. In Europe and

North America the prevalence has been estimated to be between 100 and 250 per 100 000. In Europe, prevalence rates are similar in all numberries and there is no major difference between men and women although some studies have suggested that Parkinson's disease is slightly more common among men.

The usual age of onset is after 50 years with the frequency rising steeply with age. Onset before 40 years 'Young onset Parkinson's disease' is unusual and before 20 is exceptional 'Juvenile Parkinson's disease'. Advancing age remains the most powerful predictor of developing Parkinson's disease; the lifetime risk of developing Parkinson's disease is 2 per cent for men and 1.3 per cent for women (Elbaz et al, 2002)[11].

Epidemiological studies have detected a variety of risk factors. The significance of these findings is unclear but a common thread is that Parkinson's disease might be due to exposure to an unidentified environmental toxin. Head trauma, inflammation, Caucasian ancestry, Nocardia infection are possible risk factors in case control studies. Protective factors have also been identified: smoking reduces the risk of Parkinson's disease by 60 per cent and coffee drinking by 30 per cent (Hernan ef al. 2002)[10]; alcohol and use of non-steroidal antiinflammatory drugs may also be protective.

Pathology of Parkinson's disease[9,25,26,27,28]

The basic neuropathological feature[8] is loss of pigmented dopaminergic neurones, astrocytic gliosis, dystrophic neurites, and the formation of Lewy bodies in the substantia nigra pars compacta[37,38,39]. However, other brain regions are also affected including other brainstem nuclei and the cerebral cortex. The pathological hallmark of Parkinson's disease is the Lewy body[25], an eosinophilic intracellular inclusion[8]. Typically there is a central core within a less intensely staining body surrounded by a pale, halo[37,38,39].

Clinical features

Parkinson's disease is often regarded as an easy 'end of the bed' diagnosis but is highly variable in presentation and frequently misdiagnosed (Hughes et al. 1993b)[9]. Bradykinesia causes a poverty of movement leading to an abnormal stiffness and impassive appearance. The posture becomes one of flexion of the neck, spine elbows, wrists, hips and knees. The patient stands and walks on a narrow base. Facial expression is reduced with the mouth slightly open, the voice is quiet and monotonous and later there is a greasy skin. Some patients present with minimal and

easily overlooked physical signs such as slightly reduced arm swing on one side while walking with barely noticeable wrist rigidity brought out by synkinesis of the contralateral arm; others present at a surprisingly late stage with gross Parkinsonism and considerable disability. The most characteristic presentation is with tremor, bradykinesia and rigidity of an upper limb.

The most reliable diagnostic principle is the presence of two out of the three cardinal features of:

- Tremor
- Bradykinesia and
- Rigidity

To this could be added the presence of a good response to levodopa therapy which is observed In all but a handful of patients (Hughes et al 1993b)[13].

The Parkinsonian tremor is noticeable at rest and is less prominent or absent with action or posture. The frequency is slow, 4-7 Hz, and may involve only the thumb or one finger at first. In some patients the typical 'pillrolling' appearance is seen but this is not invariable. The tremor is increased by movement of the contralateral limbs or walking. Eventually

the tremor spreads to the contralateral limbs but often remains more noticeable on the initially affected side.

Parkinsonian rigidity[8] may be a smooth resistance to passive movement, ‘lead pipe' or 'plastic' rigidity, or may have a ratchet like-cogwheel effect due to additional postural tremor. Parkinsonian rigidity is more obvious in the extremities and only later becomes prominent in the axial musculature. It is detectable with slow passive limb movement unlike spasticity which is related to rapid movement. It can be brought out by contralateral limb movement, the Froment sign[8], and a useful point ill the outpatient clinic is that the rigidity is often more noticeable at the wrist.

Bradykinesia[8] refers to the slowness of movement and is closely related to akinesia or absence of movement. There are many manifestations of bradykinesia including reduced facial expression, drooling of saliva, reduced blinking, reduced arm swing while walking, difficulty turning in bed or rising from a chair, slowness of gait and small shuffling steps. Repetitive movements show slowing and reduced amplitude; finger movements are particularly affected and become clumsy and laboured. Handwriting becomes small and spidery at an early stage, micographia. This may be a presenting symptom.

Postural instability[8] is often cited as a fourth core feature of Parkinson's disease but it is not often an early symptom. When walking there is a liability to topple forward with faster steps and difficulty stopping, festination.

Autonomic Dysfunction in Parkinson's Disease[1,2,17,19]

Autonomic dysfunction in PD patients is being recognized since the original description by James Parkinson in 1817. Although severe ANS dysfunction is

mostly seen with advanced PD, it is present in PD patients even in the early stages of the disease[21]. The symptoms of ANS dysfunction, mainly orthostatic hypotension and excessive sweating greatly compromise the quality of life of patients.

The pathologic process is seen in both the sympathetic and the parasympathetic systems as proven by the postmortem studies[37,38,39]. The peripheral ganglia of the sympathetic, parasympathetic systems and the hypothalamus are also involved. Isotope imaging techniques have shown involvement of the peripheral portions of ANS and loss of sympathetic innervation of the heart.(Goldstein *et al.* 2000)[14]. Studies on PD patients have shown that cardiovascular autonomic dysfunction occur in these patients which can be assessed by cardiovascular reflex tests[3,18].

Abnormalities noted are suppressed HR responses to breathing, the Valsalva manoeuvre and tilting, reflecting the parasympathetic dysfunction of cardiovascular control (Haapaniemi *et al.* 2000a)[15], and pronounced BP fall in response to standing, indicating of sympathetic dysfunction (Turkka *et al.* 1997)[16].

The pathology of PD not only involves dopaminergic centers but also in the autonomic nervous system[25,26,27]. Rajput and Rozdilsky[5] has noted that Lewy bodies and cell loss occurring within the sympathetic ganglia of PD patients. Antibodies to sympathetic neurons also have been detected in PD patients. The neurodegeneration of PD and Lewy bodies is also seen in other autonomic regulatory regions, like hypothalamus[28], sympathetic system (intermediolateral nucleus of the thoracic cord and sympathetic ganglia), and parasysmpathetic system (dorsal, vagal, and sacral parasympathetic nuclei. Lewy bodies were also seen in the adrenal medulla and in the neural plexi innervating the gut, heart[25,26,27]. This work provides convincing neuropathologic evidence that both the central and peripheral autonomic nervous systems can be affected in PD[37,38,39]. Autonomic symptoms are not disabling in early Stages of disease[29]. In early Stages Gastrointestinal tract autonomic symptoms are more common than genitourinary symptoms[29]. Cardiovascular symptoms are more common in Stages III TO V. In Stage I,II urinary symptoms are mild, sexual

dysfunction sweating disturbance are present[29]. In Stage III severe urinary symptoms and orthostatic hypotension are troublesome. In Stage IV AND V worsening orthostatic hypertension, sialorrhoa develops and urinary incontinence make them disabled.

Autonomic Function Tests

Autonomic function testing is gaining an important role in electro neurophysiology. A number of tests are used for evaluating the autonomic functions. The important tests are summarized.

Tests for cardiovascular autonomic system regulation

Sympathetic stimulation increases the heart rate and ionotropic action on heart, vasodilation of coronary vessels, and constriction of resistance vessels[30.31]. The parasympathetic stimulation has the opposite effect although with minimal effect on peripheral vessels. Afferent impulses originate in cardio-machanoreceptors, pulmonary stretch receptors, and arterial baroreceptors which are located in aortic arch , carotid sinus, and thoracic arteries. Regulation of cardiovascular autonomic functions occurs by a negative feedback mechanism[30,31].

Important tests used for evaluation of autonomic functions

A. Tests of cardiovascular autonomic system regulation

Cardiovascular response on standing and Heart rate variability(HRV) 30:15 R-R ratio[32,33]

Head up tilt-table testing

HRV with respiration (sinus arrhythmia; R-R-interval analysis)

Valsalva maneuver and valsalva ratio

B. Tests of thermoregulatory function

Sympathetic skin response(SSR),

Quantitative sudomotor axon reflex test(QSART)

C. Miscellaneous tests

Exocrine and regulation of pupil tests

Gastrointestinal autonomic regulation tests

Genitourinary autonomic regulation tests

Heart rate and Blood Pressure Recording[42]

Beat-to-beat heart rate analysis is useful, because of the heart rate reflexes occuring within seconds of a stimulus[32]. Heart rate can be documented on an electrocardiogram or on electromyographic equipment. For recording ECG signals on EMG equipment, the low filter should be set

at 1-5 Hz and high filter at 500 Hz; an epoch of l-2min is recorded. The active recording electrode is placed over the apex in midclavicular line and reference on lower third of sternum. Heart rate has inverse correlation with RR interval and can be easily calculated by the formula

$$\text{Heart rate (R-R/min)} = \frac{\text{Sweep speed (mm/s)}}{\text{R-R interval in mm}} \times 60$$

For this test patient should be in sinus rhythm. Patients having premature beat and succeeding pause should not be included in the analysis.

Blood pressure(BP) is recorded from standard blood pressure equipment with the level of measurement being maintained at heart level.

Cardiovascular Responses to Standing and 30:15 R-R Ratio[4,6,32,33]

Blood pressure changes on standing are studied to assess the integrity of the sympathetic system and heart rate changes of parasympathetic cholinergic (cardiovagal) functions. Normally, on standing, exercise reflex and mechanical effects on venous capacitance and arterial resistance vessels become operative in addition to gravitational changes {Ewing et al., 1976)[7]. Squeezing of capacitance. vessels by postural muscle results in displacement of blood toward heart, which

increases venous return, cardiac output, and blood pressure. These changes stimulate baroreceptors, which ensure pronounced neurally mediated reflex and reduce sympathetic outflow, release vasoconstrictor tone, decrease total peripheral resistance up to 40%, and drop of BP up to 20mmHg. These changes last for 6-8 s. Heart rate increases immediately upon standing and continues to rise for next several seconds, whereupon it slows to a maximum extent by 20 s (Ewing et al., 1976)[7].

Technique and normal values[4,43,44]

BP and Heart rate are measured after a rest of 20 minutes initially. BP and heart rate are measured at baseline and then serially for 1-3 min after standing. ECG allows determination of 30:15 R-R ratio, i.e. the longest R-R interval (slowest heart rate) occurring about 30 beats after standing divided by the shortest RR interval (fastest heart rate), which occurs about 15 beats after standing (Ewing et al., 1976)[7].

The diagnosis of orthostatic hypotension is based on a fall of at least 20mmHg systolic or 10 mm of diastolic BP on assuming erect posture but some authorities allow more than 30 mm systolic and 20 mm diastolic BP. The 30:15 R-R ratio is normally greater than 1.04 and abnormal if less than 1.0 (Ewing et al., 1976)[7]. The age-related normal values of R-R ratio are 30-49 years: 1.09; 50-65 years: 1.03.

Heart Rate Variation with Respiration (Sinus Arrhythmia, R-R Interval Analysis)[33,41,42]

The study of heart rate variation with respiration is indicated for testing the integrity of parasympathetic cholinergic functions[33]. The variation of heart rate with respiration is known as sinus arrhythmia[40,41]. Inspiration increases and expiration decreases the heart rate. Sinus arrhythmia is abolished by parasympathetic block by atropine but not affected by sympathetic blockade by betablockers. Pulmonary stretch receptors, cardiac mechanoreceptors, and possibly baroreceptors contribute to sinus arrhythmia[33,35]. It decreases with age, increases at slower respiratory rate reaching maximum around 5-6 respiration/min[40,41].

Method: A simple protocol for studying sinus arrhythmia is putting the patient supine with head elevated to 30° and breathing deeply at a rate of 6/min, allowing 5 s each for inspiration and expiration. The maximum and minimum heart rate with each respiratory cycle and mean variation are determined. Heart rate variability(HRV) ratio is determined as the sum of six longest R-R intervals, divided by the sum of six shortest R-R intervals[33,35]. Normal values for single deep breath E-I ratio at different age are 41-50 years > 1.12, 51-60 years >1.09, 61-70 years >1.07.

The advantage of studying sinus arrhythmia is that it is sensitive and can be easily carried out on most EMG equipments[33,35].

Valsalva Maneuver and Valsalva Ratio[43,44]

Valsalva maneuver helps in assessing the parasympathetic cholinergic functions. Valsalva maneuver has four phases.

Phase I:

Phase I occurs at the onset of strain. There is transient increase in BP lasting for a few seconds, because of increased intrathoracic pressure and mechanical squeeze of the great vessels. The heart rate, does not change in this phase.

Phase II:

Phase II occurs during straining. In the early part, the venous return decreases resulting in reduction of stroke volume, cardiac output, and thus BP, which lasts for 4 s. In later part of phase II, BP returns toward baseline. This recovery occurs due to increased sympathetic vasoconstriction. Throughout phase II, the heart rate increases steadily, which is due to vagal withdrawal in the early and increased sympathetic activity in later part of stage II.

Phase III:

Phase III occurs following release of strain which results in transient decrease of BP lasting for a few seconds which is due to mechanical displacement of blood to pulmonary circulation, which was under increased intrathoracic pressure.

Phase IV:

Phase IV occurs with stopping of strain. The BP slowly increases and HR decreases. As the BP rises to above and the HR falls below baseline level, it is called overshoot phenomenon. It occurs following 15-20s after release of strain and may last for 1 min or longer. The overshoot phenomenon is due to increase in venous return, stroke volume, and cardiac output. Valsalva ratio is the ratio of maximum heart rate in phase II to minimal heart rate in phase IV and can be calculated as the longest R-R interval during phase IV to the shortest R-R interval of phase II.

Method :

The patient lies supine with head elevated to 30°. The patient strains for 15 s against by blowing 40 mmHg through a mouthpiece to a sphygmomanometer. Following stopping of the valsalva strain, the patient relaxes and breathes normally. The ECG is monitored during the strain

and 30-45s following its release. The maximum heart rate of phase II actually occurs about 1 s following cessation of strain, which is generally taken as the maximum heart rate. The minimum heart rate occurs about 15-20s after releasing the strain. The ratio of maximum to minimum heart rate is calculated by repeating the procedure 3 times.

Miscellaneous Tests

Blood Pressure Response to Isovolumetric exercise :

Sustained muscular contraction causes increased BP and heart rate as a result of exercise reflex, which reduces parasympathetic and increases sympathetic activity. Sympathetic adrenergic function is responsible for blood pressure changes and the parasympathetic cholinergic function is responsible for HR changes. In this test, the patient maintains a grip of 30% of maximum voluntary activity for 3-5 min. Normally, the diastolic BP will rise more than 15 mmHg. This test is relatively independent of age (Ewing et al., 1976)[7].

Blood Pressure To Mental Arithmetic[43 44]

Blood Pressure Response to Mental Stress such as arithmetic, sudden noise or emotional stress can result in increase in BP and heart rate

due to excessive sympathetic outflow. It is a useful test of sympathetic efferent function.

Cold Pressor Test[43,44]

The patient submerges one upper limb in ice cold water for 60s, which results in rise of systolic BP by 15-20 mmHg and diastolic by 10 mmHg. The afferent limb of the test is somatic and efferent sympathetic.

MATERIALS AND METHODS

MATERIALS AND METHODS

The study was conducted in Institute of Neurology Madras Medical College Chennai during 2011 to 2013. The study had been approved by Ethical Committee of Medical Faculty Madras Medical College Chennai. Informed and written consent were obtained in patient's own language before their inclusion in the study. 141 patients fulfilling the criteria of Parkinson's disease brain bank society[8,37] were included in the study. They constitute both the outpatients and inpatients of our hospital. The Study design is cross sectional study.

Inclusion Criteria :

All the patients fulfilling the criteria of Parkinson's disease society brain bank were included in the study.

Exclusion Criteria :

All the patients with other central or peripheral nervous system disease, Parkinson plus syndromes, systemic diseases and drugs that are known to cause ANS dysfunction were excluded from the study**.**

The patients were diagnosed based on the following Parkinson's disease society brain bank criteria[8,37].

Parkinson's disease society brain bank criteria[8,37]

1. Criteria required to establish the presence of Parkinsonism	Bradykinesia Plus one of the following: Rigidity Resting tremor Postural instability
2. Exclusion criteria for Parkinson's disease	Repeated stroke or stepwise progression Repeated head injury Encephalitis Oculogyric crises Recent neuroleptic treatment Relevant toxic exposute > 1 affected relative Sustained remission of symptoms Unilateral signs aftet 3 years

	Supranuclear gaze palsy Cerebellar signs Severe, early autonomic failure Severe, early dementia Pyramidal signs Mass lesion or hydrocephalus on CT scan No response to levodopa
3. Positive criteria for Parkinson's disease (3 or more required)	Unilateral onset Rest tremor Progressive disorder Persistent asymmetry Excellent (70-100%) response to levodopa Severe levodopa induced dyskinesia Response to levodopa lasting >5 years Clinical course over > 10 years

All the patients were clinically examined with special attention to history, clinical features and symptoms and signs of Autonomic dysfunction. The patients were graded using the Hoehn and Yahr staging system.

Hoehn And Yahr Staging[1]

Stage I : Only unilateral involvement, usually with minimal or no functional disability.

Stage II : Bilateral disease or midline involvement without impairment of balance.

Stage III : Mild to moderate bilateral disease with impaired postural reflexes; physically independent.

Stage IV : Severe disabling disease; still able to walk or stand unassisted.

Stage V : Wheel chair bound or confinement to bed unless aided.

All the patients were questioned about autonomic symptoms under various categories gastrointestinal, urinary, cardiovascular, thermoregulatory and sexual dysfunction and tabulated based on their presence. A number of drugs influence the results of autonomic testing such as anticholinergics adrenergic antagonists (β-blocker), sympathomimetic, parasympathomimetic, and drugs. affecting blood volume (diuretics and fludrocortisone). These drugs were discontinued before autonomic testing in consultation with the primary physician. The patient abstained from

alcohol, tea, and coffee for at least 3 hour and preferably 12 hour.

Patient were examined in rested and relaxed condition. All patients were subjected to complete general and neurological examination, Compressive dressings such as elastic stocking were removed before the test. Patients with heart failure, obstructive lung disease, atrial fibrillation, and sicca syndrome were excluded. The following cardiovascular autonomic function tests were done for all the patients after excluding other causes.

Autonomic Function Tests

1.Blood Pressure In Supine And Standing After 3 Minutes

Abnormal: Postural fall of SBP > 20 mm of Hg AND DBP >10 mm of Hg

2. Blood Pressure Response To Sustained Handgrip

Abnormal: DBP <10 mm of Hg Normal: DBP >15 mm of Hg

3. BP Variation To Mental Arithmetic

Abnormal: DBP <10 mm of Hg Normal: DBP >15 mm of Hg

4. BP Variation To Cold Pressor test

Abnormal: DBP <5 mm of Hg Normal: DBP >10 mm of Hg

5. Heart Rate Variability Ratio To standing

Abnormal: < 1.04

6. Heart Rate Variability Ratio To Valsalva

Abnormal: <1.2

7. Heart Rate Variability Ratio To Deep Breathing

Abnormal : <1.0

The following results were considered as abnormal in cardiovascular autonomic function tests.

Valsalva ratio of less than 1.2 is regarded as abnormal, 1.2-1.45 as borderline and greater than 1.45 as normal (Ewing, 1976). Valsalva ratio decreases with age. The age specific norms are more precise: 41-60 years > 1.45, 61-70 years >1.35 (Low, 2004)[43,44]

Normal values for single deep breath E-I ratio at different age are 41-50 years > 1.12, 51-60 years >1.09, 61-70 years >1.07.

Patients with ANS system were graded in severity depending on the number of systems involved. The systems include gastrointestinal, urinary, cardiovascular, thermoregulatory and sexual dysfunction, The results were graded as follows.

Mild : Involvement of One to two systems

Moderate: Involvement of Three systems

Severe: Involvement of More than three systems

The results were analysed through SPSS version 20 (Statistical Package for the Social Sciences or Superior Performing Statistical Software) statistical analysis by Pearson Chi-square test and p values obtained.

RESULTS

OBSERVATION AND RESULTS

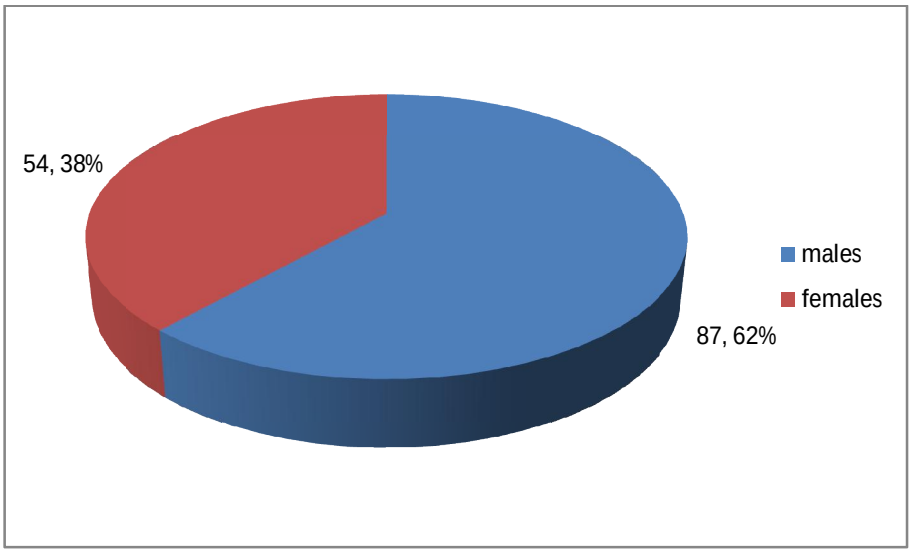
A total of 141 patients of Parkinson's disease, both inpatients and outpatients of Rajiv Gandhi Govt. General Hospital, Institute Of Neurology Madras Medical College between 2011 to 2013, were analysed and the results of analysis are as follows

1. Sex Distribution:

Among 141 patients enrolled 87 were males and 54 were females

MALES	87
FEMALES	54
TOTAL	141

Figure 1:SEXWISE DISTRIBUTION OF PATIENTS

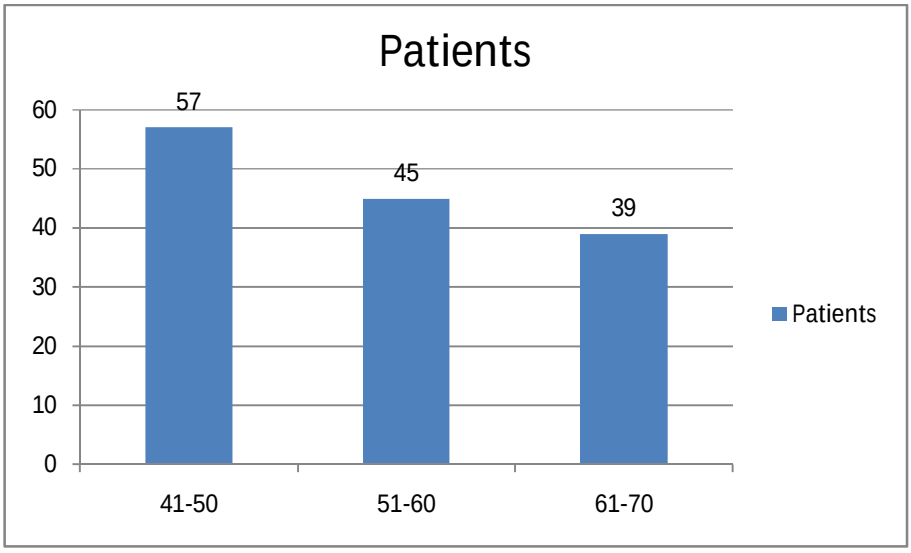


2. Age Distribution:

The mean age of male patients was 54 years, and female was 52 years. The highest age among male patients was 70 and the lowest age was 40. The patients were grouped as follows

Age (Years)	Patients	Percentage(%)
41-50	57	40.4%
51-60	45	31.9%
61-70	39	27.7%
Total	141	100%

Figure 2: AGE GROUP WISE DISTRIBUTION



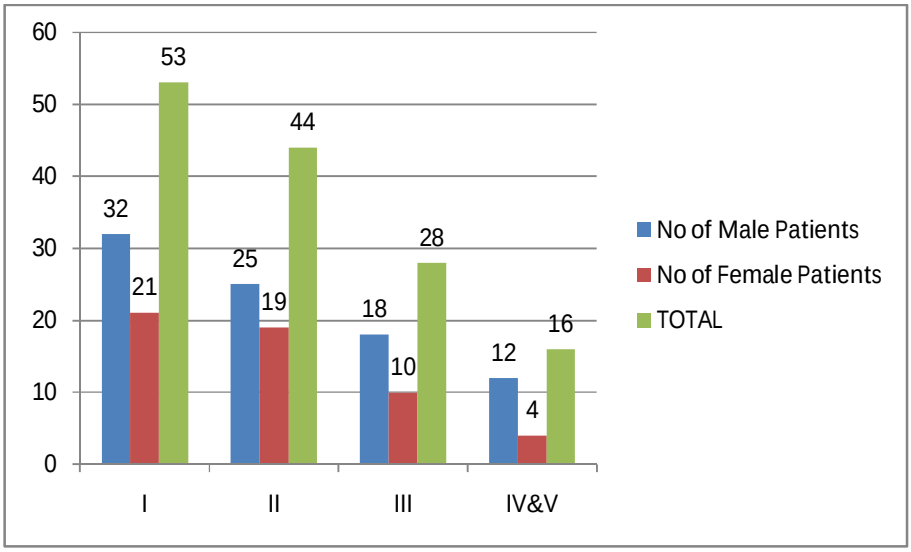
3. Hoehn and Yahr Staging of patients:

Patients were classified based on Hoehn and Yahr staging Stage I to V. Stage IV AND V were grouped into onem as the number of patients was less .

53 patients viz 32 males and 21 females belonged to Stage I of Parkinson's Disease; 44 patients viz 25 males and 19 females belonged to Stage II of Parkinson's Disease; 28 patients viz 18 males and 10 females belonged to Stage III of Parkinson's Disease; 16 patients viz 12 males and 4 females belonged to Stage IV of Parkinson's Disease.

Staging	No of Male Patients	No of Female Patients	Total
Stage I	32	21	53
Stage II	25	19	44
Stage III	18	10	28
Stage IV & V	12	4	16
Total	87	54	141

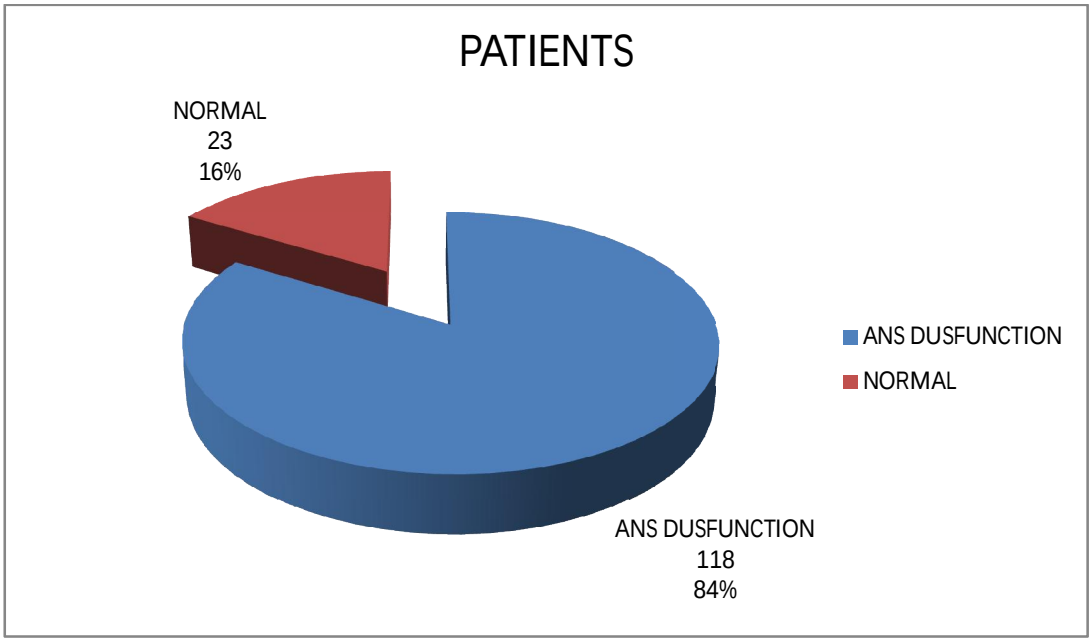
Figure 3: STAGE WISE SEX DISTRIBUTION OF PATIENTS



4. Prevalence of patients with ANS dysfunction

Among 141 patients, 118(83.7%) had autonomic dysfunction.

Figure 4: Prevalence of patients with ANS dysfunction

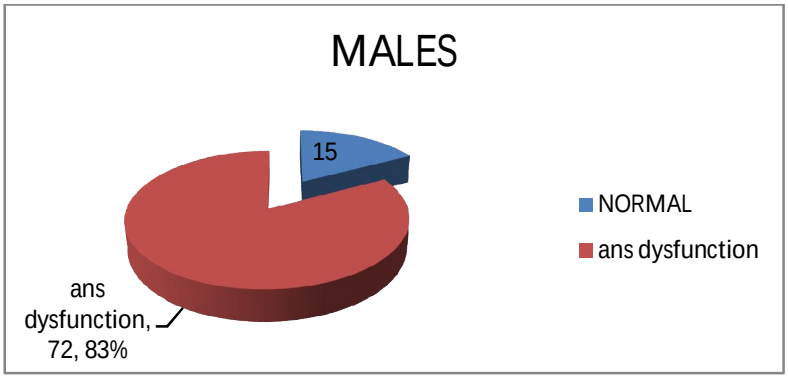


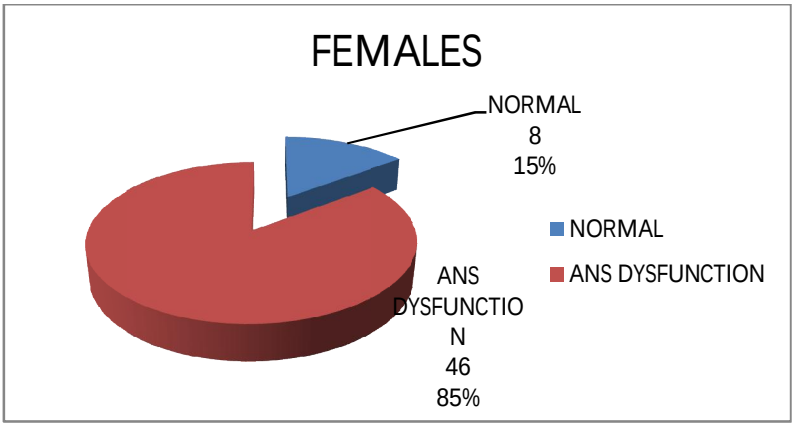
5. Sex distribution of PD Patients Having ANS Dysfunction

Among 87 males, 72 patients had ANS dysfunction and among 54 females, 46 patients had ANS dysfunction.

SEX	Total PD Patients	Patients With ANS Dysfunction
MALES	87	72(82.75%)
FEMALES	54	46(85.2%)
TOTAL	141	118(83.7%)

Figure 5: SEX DISTRIBUTION OF ANS DYSFUNCTION



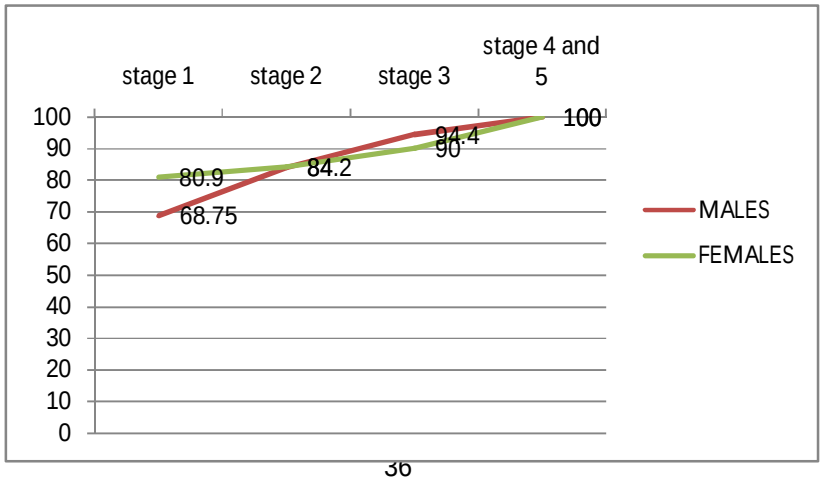


6. Stagewise distribution of PD Patients With ANS Dysfunction

Stage wise 39 of 53 patients(73.6%) belonging to Stage I; 37 of 44 (84.1%) belonging to Stage II; 26 of 28 (84.1%) belonging to Stage III and all patients belonging to Stage IV and V had ANS dysfunction.

Staging	Total No. Of Patients	Patients With ANS Dysfunction	% Of Patients With ANS Dysfunction
Stage I	53	39	73.6%
Stage II	44	37	84.1%
Stage III	28	26	92.9%
Stage IV and V	16	16	100%
Total	141	118	83.7%

Figure 6: Depicts increasing prevalence of ANS dysfunction as stage increases

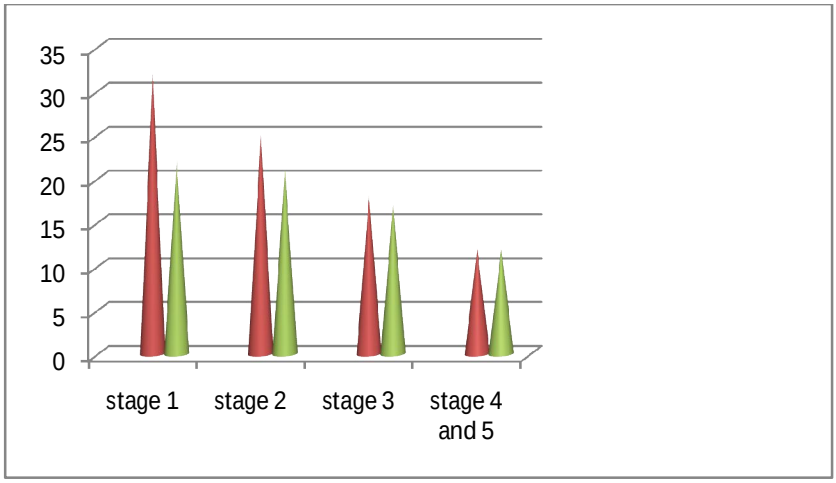


7. Stage wise Prevalence Of Male PD Patients With ANS Dysfunction:

Among male patients, 22 out of 32 belonging to Stage I of PD, 21 out of 25 belonging to Stage II, 17 out of 18 belonging to Stage III and all patients of Stage IV and V(100%) had autonomic dysfunction.

Staging	Total No. Of Males	Patients With Ans Dysfunction	% Of Males With Ans Dysfunction
Stage I	32	22	68.75%
Stage II	25	21	84.00%
Stage III	18	17	94.40%
Stage IV and V	12	12	100%
Total	87	72	82.75%

Figure 7: Stagewise Prevalence of male PD Ppatients with ANS dysfunction

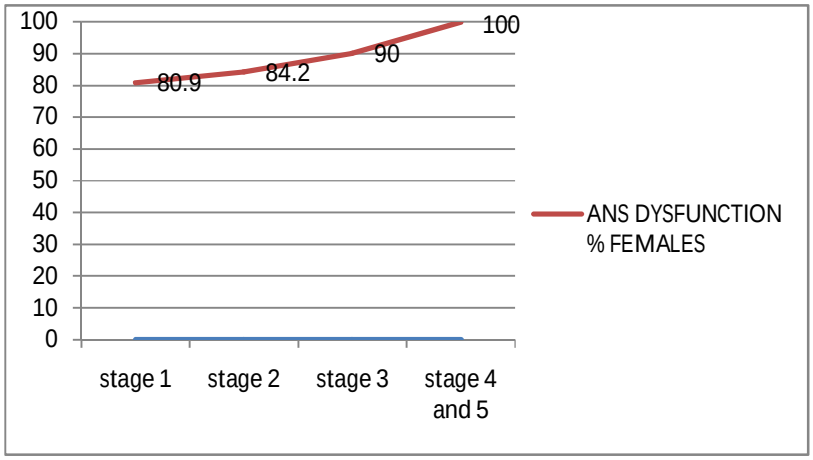


8. Stagewise Prevalence Of Female PD Patients With ANS Dysfunction

Among female patients, 17 out of 21 belonging to Stage I; 16 out of 19 belonging to Stage II, 9 out of 10 belonging to Stage III and all patients of Stage IV(100%) had autonomic dysfunction.

Staging	Total No. Of Females	Patients With Ans Dysfunction	% Of Females With Ans Dysfunction
Stage I	21	17	80.9%
Stage II	19	16	84.2%
Stage III	10	9	90%
Stage IV& V	4	4	100%
Total	54	46	90.7%

Figure 8: Stagewise Prevalence Of Female PD Patients With ANS Dysfunction

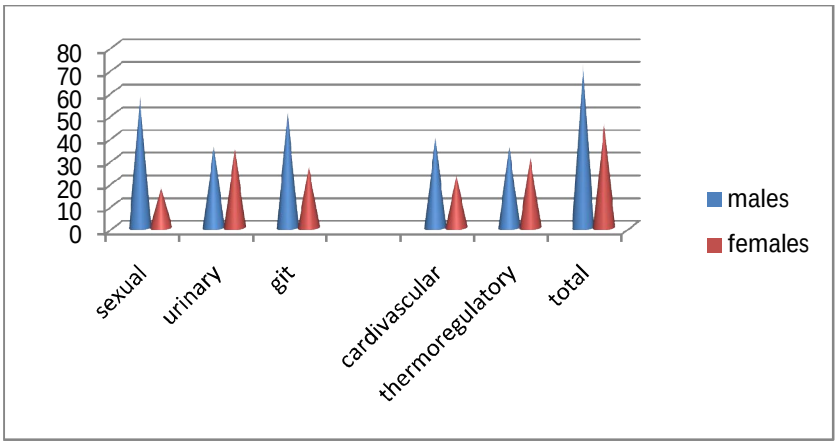


9. Prevalence Of Systemwise distribution of ANS Dysfunction in PD Patients:

Among 118 patients, 61male and 21 female had sexual dysfunction, 34 males and 36 females had urinary dysfunction, 41 males and 22 females had gastrointestinal tract dysfunction, 27 males and 26 females had cardiovascular dysfunction, 37 males and 30 females had thermoregulatory dysfunction. Patients had ANS dysfunction in multiple categories.

Categories	Males	Females
Sexual	61(84.7%)	21(45.7%)
Urinary	34(47.2%)	36(78.3%)
GIT	41(56.9%)	22(47.8%)
Cardiovascular	27(37.5%)	26(56.5%)
Thermoregulatory	37(51.3%)	30(65.2%)

Figure 9: PREVALENCE OF SYSTEMWISE ANS DYSFUNCTION IN PD PATIENTS BOTH MALES AND FEMALES

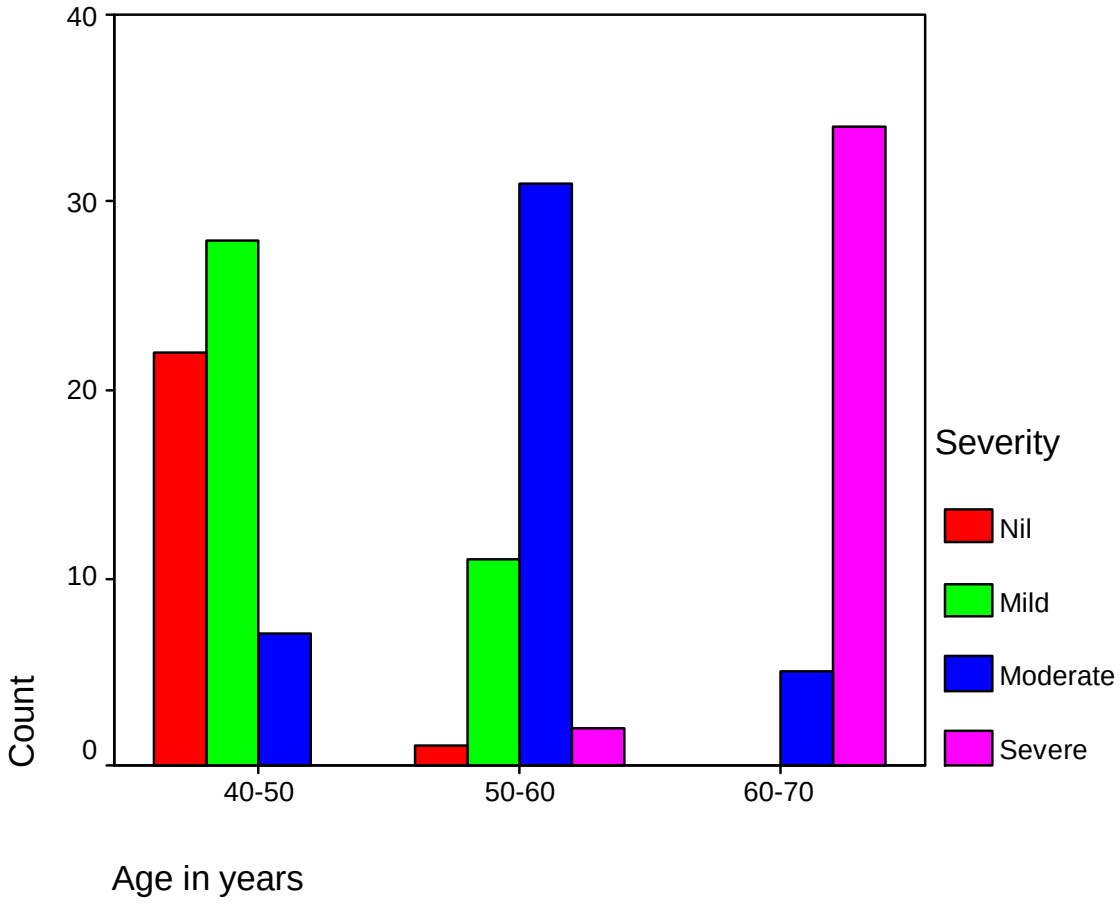


10. Age Correlation With Severity Of ANS Dysfunction

In 40-50 years age group, 38.6% (n-22) did not have ANS dysfunction; 49.1% had mild ANS dysfunction ; 12.3% had moderate ANS dysfunction ; none had severe ANS dysfunction. But on the contrary in 60-70 age group, 12.8% had moderate ANS dysfunction and 94.4% severe ANS dysfunction. The results are tabulated as follows:

			Severity				Total	
			Nil	Mild	Moderate	Severe		P VALUE
Age in years	40-50	Number	22	28	7	0	57	
		% of patients within same Age group	38.6%	49.1%	12.3%	.0%	100.0%	<0.0001
		% of patients within same severity grading	95.7%	71.8%	16.3%	.0%	40.4%	<0.0001
	50-60	Number	1	11	31	2	45	
		% of patients within same Age group	2.2%	24.4%	68.9%	4.4%	100.0%	<0.0001
		% of patients within same severity grading	4.3%	28.2%	72.1%	5.6%	31.9%	<0.0001
	60-70	Number	0	0	5	34	39	
		% of patients within same Age group	.0%	.0%	12.8%	87.2%	100.0%	<0.0001
		% of patients within same severity grading	.0%	.0%	11.6%	94.4%	27.7%	<0.0001
Total		Number	23	39	43	36	141	
		% of patients within same Age group	16.3%	27.7%	30.5%	25.5%	100.0%	

FIG 10: **Age Correlation With Severity Of ANS Dysfunction**



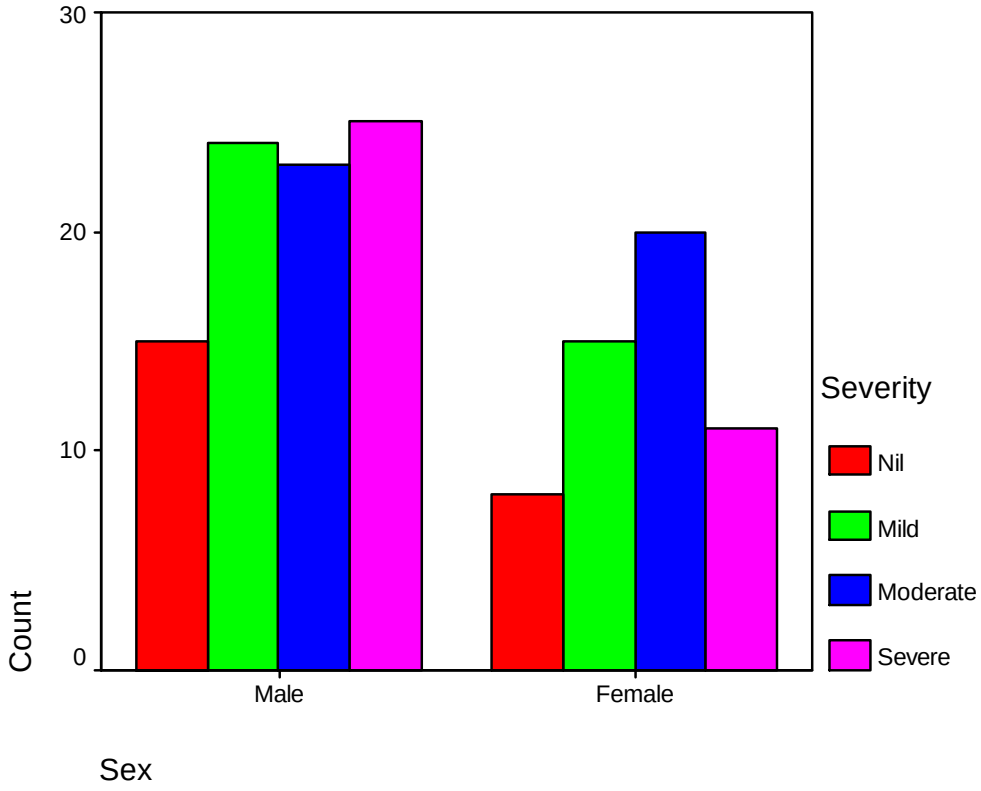
11. Sex Correlation With Severity Of ANS Dysfunction

On analysing sex distribution with severity of dysfunction, among males 17.2% (n-15) did not have ANS dysfunction; 27.6% (n-24) had mild ANS dysfunction ; 26.4%(n-23) had moderete ANS dysfunction ;

28.7%(n-25) had severe ANS dysfunction. In females 14.8% (n-8) did not have ANS dysfunction; 27.8% (n-15) had mild ANS dysfunction ; 37.0%(n-20) had moderete ANS dysfunction ; 20.4%(n-11) had severe ANS dysfunction The results are tabulated as follows:

			Severity				Total
			Nil	Mild	Moderate	Severe	
Sex	Male	Number	15	24	23	25	87
		% of patients within same sex	17.2%	27.6%	26.4%	28.7%	100.0%
		% of patients within same severity grading	65.2%	61.5%	53.5%	69.4%	61.7%
	Female	Number	8	15	20	11	54
		% of patients within same sex	14.8%	27.8%	37.0%	20.4%	100.0%
		% of patients within same severity grading	34.8%	38.5%	46.5%	30.6%	38.3%
Total		Number	23	39	43	36	141
		% of patients within same sex	16.3%	27.7%	30.5%	25.5%	100.0%

FIG 11: **Sex Correlation With Severity Of ANS Dysfunction(p <0.05)**

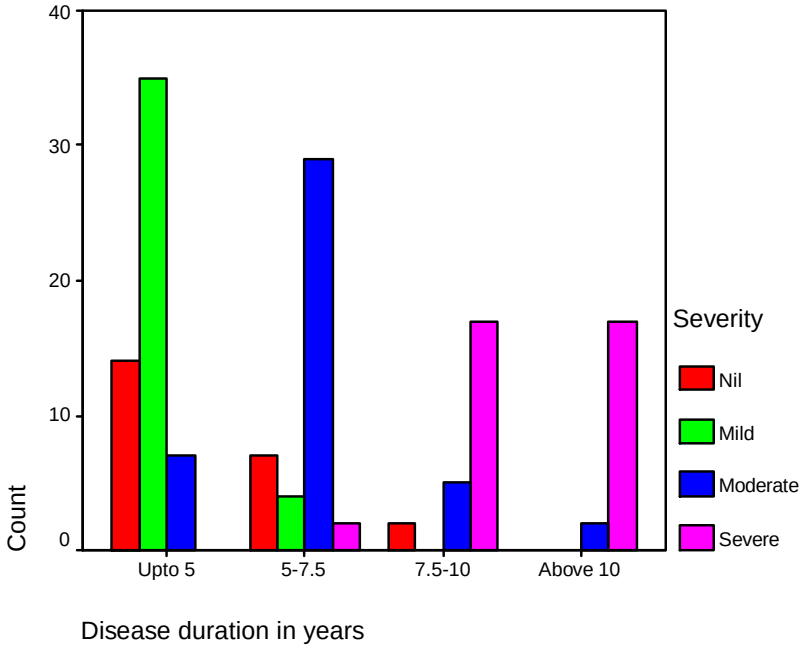


12. Disease Duration In Years Correlation With Severity Of ANS Dysfunction

The results of correlation of duration of PD with severity of ANS dysfunction were tabulated as follows.

			Severity of ANS dysfunction				Total	
			Nil	Mild	Moderate	Severe		P VALUE
Disease duration in years	Upto 5	number	14	35	7	0	56	
		% of patients with ANS dysfunction within same duration group	25.0%	62.5%	12.5%	.0%	100.0%	<0.0001
		% of patients within same severity grading	60.9%	89.7%	16.3%	.0%	39.7%	<0.0001
	5-7.5	Number	7	4	29	2	42	
		% of patients ANS dysfunction within same duration group	16.7%	9.5%	69.0%	4.8%	100.0%	<0.0001
		% of patients within same severity grading	30.4%	10.3%	67.4%	5.6%	29.8%	<0.0001
	7.5-10	Number	2	0	5	17	24	
		% of patients with ANS dysfunction within same duration group	8.3%	.0%	20.8%	70.8%	100.0%	<0.0001
		% of patients within same severity grading	8.7%	.0%	11.6%	47.2%	17.0%	<0.0001
	Above 10	Number	0	0	2	17	19	
		% of patients with ANS dysfunction within same duration group	.0%	.0%	10.5%	89.5%	100.0%	<0.0001
		% of patients within same severity grading	.0%	.0%	4.7%	47.2%	13.5%	<0.0001
Total		Number	23	39	43	36	141	
		% of patients within same duration group	16.3%	27.7%	30.5%	25.5%	100.0%	

12. Disease Duration In Years Correlation With Severity Of ANS Dysfunction

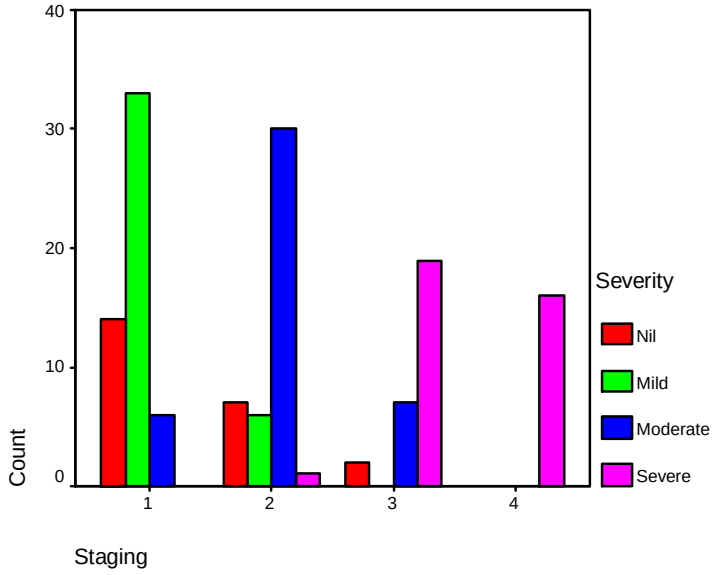


13. Hoehn And Yahr Stage Wise Severity Of Dysfunction

The results of correlation of Hoehn and Yahr stage with severity of ANS dysfunction were tabulated as follows.

			Severity				Total	
			Nil	Mild	Moderate	Severe		P value
Staging	I	Number	14	33	6	0	53	
		% of patients with ANS dysfunction within same Staging	26.4%	62.3%	11.3%	.0%	100.0%	<0.0001
		% of patients within same severity grading	60.9%	84.6%	14.0%	.0%	37.6%	<0.0001
	II	Number	7	6	30	1	44	
		% of patients with ANS dysfunction within same Staging	15.9%	13.6%	68.2%	2.3%	100.0%	<0.0001
		% of patients within same severity grading	30.4%	15.4%	69.8%	2.8%	31.2%	<0.0001
	III	Number	2	0	7	19	28	
		% of patients with ANS dysfunction within same Staging	7.1%	.0%	25.0%	67.9%	100.0%	<0.0001
		% of patients within same severity grading	8.7%	.0%	16.3%	52.8%	19.9%	<0.0001
	IV & V	Number	0	0	0	16	16	
		% of patients with ANS dysfunction within same Staging	.0%	.0%	.0%	100.0%	100.0%	<0.0001
		% of patients within same severity grading	.0%	.0%	.0%	44.4%	11.3%	<0.0001
Total		Number	23	39	43	36	141	
		% of patients within same Staging	16.3%	27.7%	30.5%	25.5%	100.0%	<0.0001
		% of patients within same severity grading	100.0%	100.0 %	100.0%	100.0%	100.0%	<0.0001

FIG 13: **Stagewise Correlation With Severity Of ANS Dysfunction depicting more severity in stage III and IV**



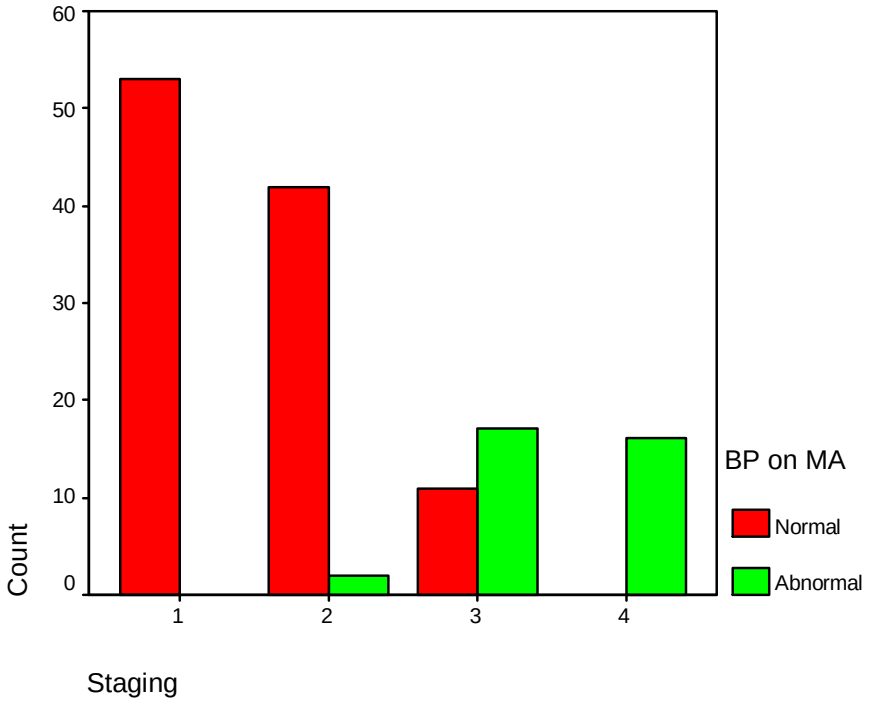
14.Correlation Of Individual Autonomic Function Tests With Staging

14.a. Abnormal BP On Mental Arithmetic

The results of BP on Mental Arithmetic were correlated with staging of disease and tabulated as follows.

			Response of BP on Mental arithmetic		Total	
			Normal	Abnormal		p value
Staging	I	Number	53	0	53	
		% of patients within same Staging	100.0%	.0%	100.0%	<0.0001
		% of patient within same response	50.0%	.0%	37.6%	<0.0001
	II	Number	42	2	44	
		% of patients within same Staging	95.5%	4.5%	100.0%	<0.0001
		% of patient within same response	39.6%	5.7%	31.2%	<0.0001
	III	Number	11	17	28	
		% of patients within same Staging	39.3%	60.7%	100.0%	<0.0001
		% of patient within same response	10.4%	48.6%	19.9%	<0.0001
	IV & V	Number	0	16	16	
		% of patients within same Staging	.0%	100.0%	100.0%	<0.0001
		% of patient within same response	.0%	45.7%	11.3%	<0.0001
Total		Number	106	35	141	
		% of patients within same Staging	75.2%	24.8%	100.0%	

FIG 14a: STAGING CORRELATION WITH ABNORMAL BP ON MENTAL ARITHMETIC

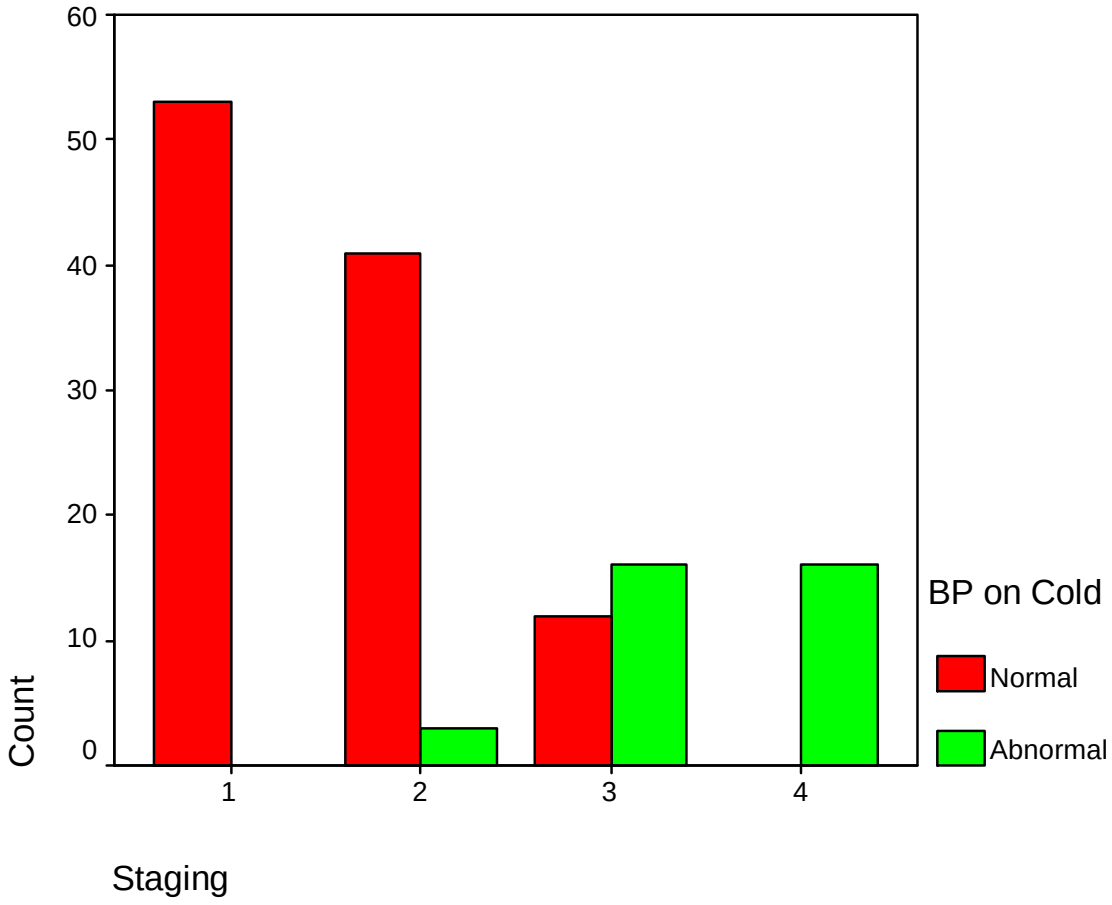


14.b. Correlation With Abnormal BP On Cold Pressor Test

The results of BP on Cold pressor test were correlated with staging of disease and tabulated as follows.

			Response of BP on Cold		Total	
			Normal	Abnormal		p value
Staging	I	Number	53	0	53	
		% of patients within same Staging	100.0%	.0%	100.0%	<0.0001
		% of patient within same response	50.0%	.0%	37.6%	<0.0001
	II	Number	41	3	44	
		% of patients within same Staging	93.2%	6.8%	100.0%	<0.0001
		% of patient within same response	38.7%	8.6%	31.2%	<0.0001
	III	Number	12	16	28	
		% of patients within same Staging	42.9%	57.1%	100.0%	<0.0001
		% of patient within same response	11.3%	45.7%	19.9%	<0.0001
	IV & V	Number	0	16	16	
		% of patients within same Staging	.0%	100.0%	100.0%	<0.0001
		% of patient within same response	.0%	45.7%	11.3%	<0.0001
Total		Number	106	35	141	
		% of patients within same Staging	75.2%	24.8%	100.0%	

Fig 14b: Stage Wise Correlation With Abnormal BP On Cold Pressor Test



14.c. Stage Wise Correlation With BP On Standing

The results of BP on standing were correlated with staging of disease and tabulated as follows.

			Response of BP on Standing		Total	
			Normal	Abnormal		p value
Staging	I	Number	53	0	53	
		% of patients within same Stage	100.0%	.0%	100.0%	<0.0001
		% of patient within same response	50.0%	.0%	37.6%	<0.0001
	II	Number	42	2	44	
		% of patients within same Staging	95.5%	4.5%	100.0%	<0.0001
		% of patient within same response	39.6%	5.7%	31.2%	<0.0001
	III	Number	10	18	28	
		% of patients within same Staging	35.7%	64.3%	100.0%	<0.0001
		% of patient within same response	9.4%	51.4%	19.9%	<0.0001
	IV & V	Number	1	15	16	
		% of patients within same Staging	6.3%	93.8%	100.0%	<0.0001
		% of patient within same response	.9%	42.9%	11.3%	<0.0001
Total		Number	106	35	141	
		% of patients within same Staging	75.2%	24.8%	100.0%	

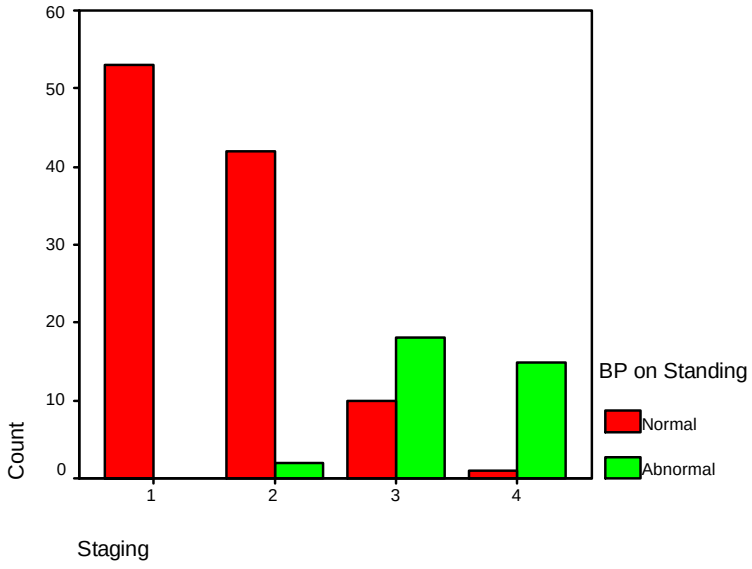


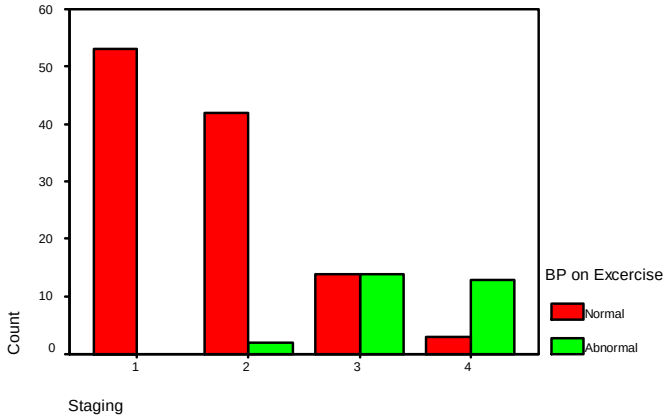
FIG 14c: Stage Wise Correlation With BP On Standing depicting abnormality worsens as stage increases

14.d. Correlation With BP On Isovolumetric Exercise

The results of BP on isovolumetric exercise were correlated with staging of disease and tabulated as follows.

			Response of BP on isovolumetric Excercise		Total	
			Normal	Abnormal		p value
Staging	I	Number	53	0	53	
		% of patients within same Staging	100.0%	.0%	100.0%	<0.0001
		% of patient within same response	47.3%	.0%	37.6%	<0.0001
	II	Number	42	2	44	
		% of patients within same Staging	95.5%	4.5%	100.0%	<0.0001
		% of patient within same response	37.5%	6.9%	31.2%	<0.0001
	III	Number	14	14	28	
		% of patients within same Staging	50.0%	50.0%	100.0%	<0.0001
		% of patient within same response	12.5%	48.3%	19.9%	<0.0001
	IV & V	Number	3	13	16	
		% of patients within same Staging	18.8%	81.3%	100.0%	<0.0001
		% of patient within same response	2.7%	44.8%	11.3%	<0.0001
Total		Number	112	29	141	
		% of patients within same Staging	79.4%	20.6%	100.0%	

Fig 14d: Stage Wise Correlation With BP On Isovolumetric Exercise depicting more normality in stages I and II, more abnormality in stage III and IV



14.e. Correlation With HRV On Standing

The results of heart rate variability were correlated with staging of disease. 53 patients(100%) had normal HRV in stage I, whereas in stage IV and V, only 6.2% had normal HRV and 93.8%% had abnormal HRV on standing. The results are tabulated as follows.

			Response of HRV on standing		Total	
			Normal	Abnormal		P value
Staging	I	Number	53	0	53	
		% of patients within same Staging	100.0%	.0%	100.0%	<0.0001
		% of patient within same response	54.1%	.0%	37.6%	<0.0001
	II	Number	36	8	44	
		% of patients within same Staging	81.8%	18.2%	100.0%	<0.0001
		% of patient within same response	36.7%	18.6%	31.2%	<0.0001
	III	Number	8	20	28	
		% of patients within same Staging	28.6%	71.4%	100.0%	<0.0001
		% of patient within same response	8.2%	46.5%	19.9%	<0.0001
	IV V	Number	1	15	16	
		% of patients within same Staging	6.3%	93.8%	100.0%	<0.0001
		% of patient within same response	1.0%	34.9%	11.3%	<0.0001
Total		Number	98	43	141	
		% of patients within same Staging	69.5%	30.5%	100.0%	

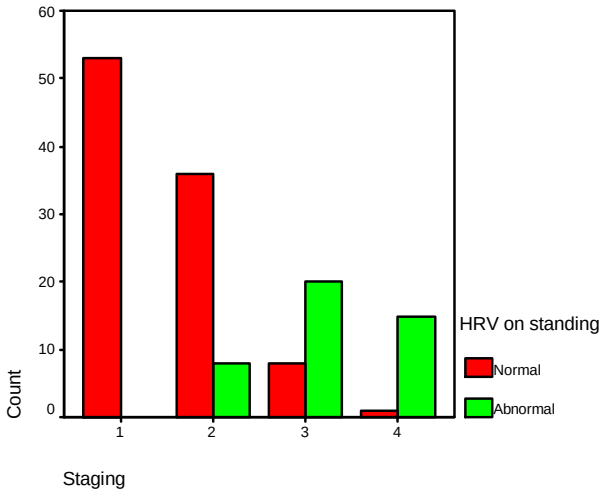


Fig 14g: Stage Wise Correlation With HRV On standing depicting more normal ratio in stages I and II, more abnormal HRV in stage III and IV

14.f. Correlation With heart rate variability On Valsalva

The results of BP on HRV on vasalva were correlated with staging of disease and tabulated as follows.

			Resonse of HRV on Valsalva		Total	
			Normal	Abnormal		P value
Staging	1	Number	53	0	53	
		% of patients within same Staging	100.0%	.0%	100.0%	<0.0001
		% of patient within same response	53.5%	.0%	37.6%	<0.0001
	2	Number	39	5	44	
		% of patients within same Staging	88.6%	11.4%	100.0%	<0.0001
		% of patient within same response	39.4%	11.9%	31.2%	<0.0001
	3	Number	7	21	28	
		% of patients within same Staging	25.0%	75.0%	100.0%	<0.0001
		% of patient within same response	7.1%	50.0%	19.9%	<0.0001
	4	Number	0	16	16	
		% of patients within same Staging	.0%	100.0%	100.0%	<0.0001
		% of patient within same response	.0%	38.1%	11.3%	<0.0001
Total		Number	99	42	141	
		% of patients within same Staging	70.2%	29.8%	100.0%	

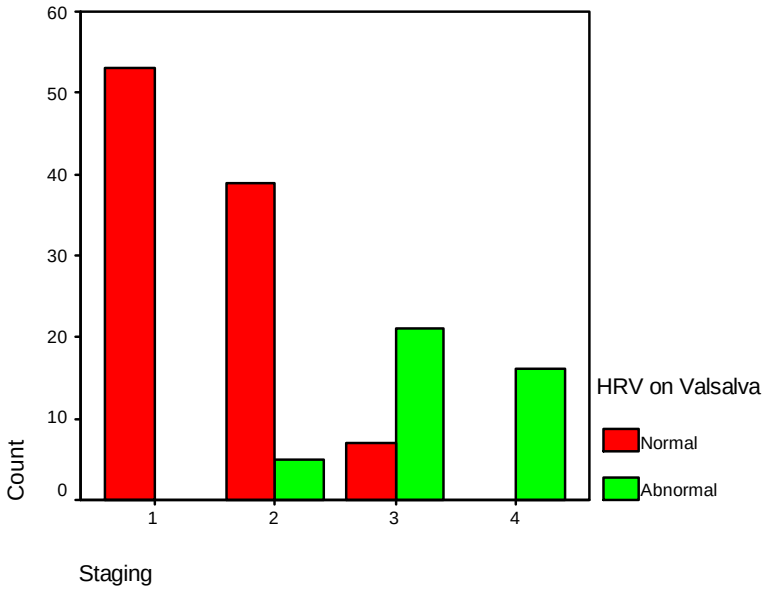


Fig 14f: Stage Wise Correlation With HRV On Valsalva depicting more normal ratio in stages I and II, more abnormal HRV in stage III and IV

14.g. Correlation With Heart rate variability On Respiration

The results of BP on HRV on respiration were correlated with staging of disease and tabulated as follows.

			Response of HRV on Respiration		**Total**	
			Normal	**Abnormal**		**P value**
Staging	**I**	**Number**	**53**	**0**	**53**	
		% of patients within same Staging	100.0%	.0%	100.0%	<0.0001
		% of patient within same response	53.0%	.0%	37.6%	<0.0001
	II	Number	38	6	44	
		% of patients within same Staging	86.4%	13.6%	100.0%	<0.0001
		% of patient within same response	38.0%	14.6%	31.2%	<0.0001
	III	Number	8	20	28	
		% of patients within same Staging	28.6%	71.4%	100.0%	<0.0001
		% of patient within same response	8.0%	48.8%	19.9%	<0.0001
	IV & V	Number	1	15	16	
		% of patients within same Staging	6.3%	93.8%	100.0%	<0.0001
		% of patient within same response	1.0%	36.6%	11.3%	<0.0001
Total		Number	100	41	141	
		% of patients within same Staging	70.9%	29.1%	100.0%	

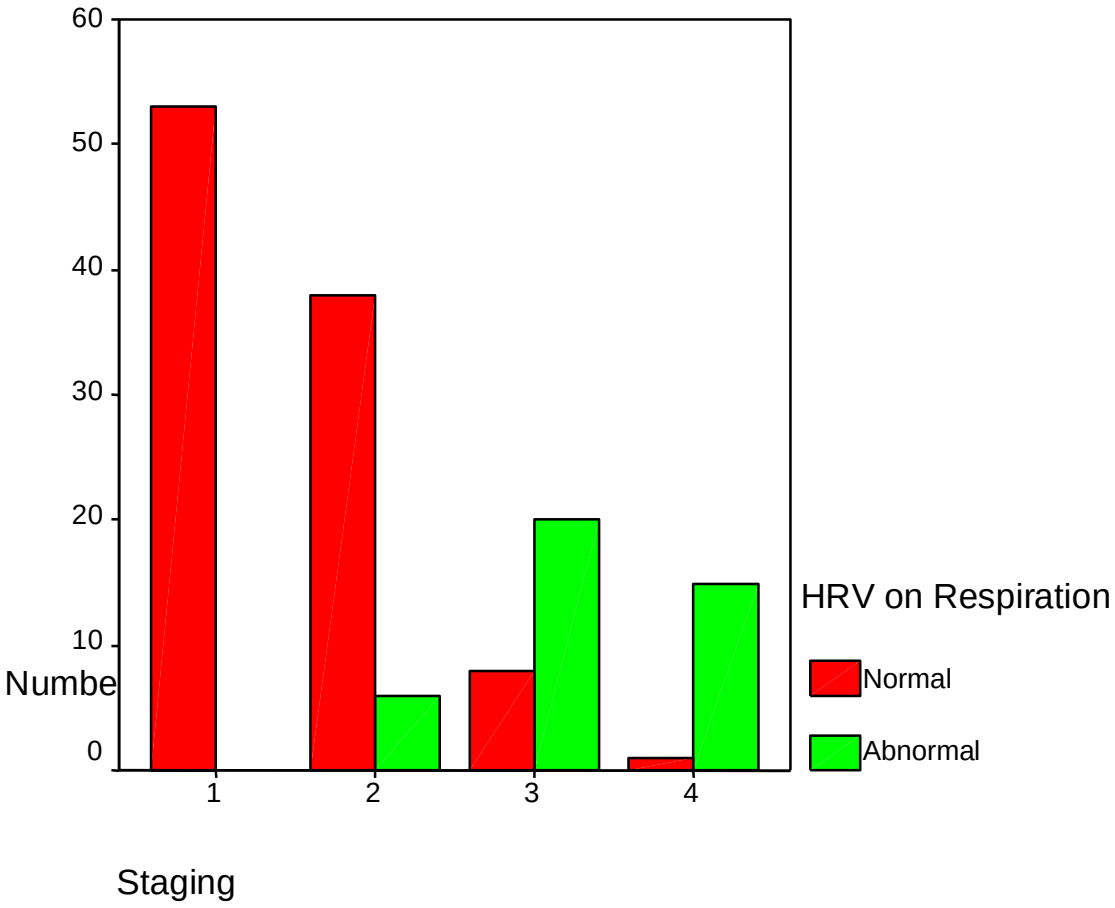


Fig 14g: Stage Wise Correlation With HRV On respiration depicting more abnormal ratio in stage III and IV.

DISCUSSION

DISCUSSION

A total of 141 patients both inpatients and outpatients of Rajiv Gandhi Govt. General Hospital, Institute Of Neurology Madras Medical College between 2011 and 2013 with clinical feature suggestive of Parkinson's Disease were analysed.

Among 141 patients enrolled in the study 87 were males and 54 were females with the ages ranging from 40-70 years in males and females,

The mean age of males and females were 54 years and 52 years respectively. 57(40.4%) of patients were in the age group of 40years to 50 years; 45(31.9%) of patients were in the age group of 51 years to 60 years; 39(27.7%) of patients were in the age group of 61 years to 70 years.

On classification based on staging, 53 patients viz 32 males and 21 females belonged to Stage I of Parkinson's Disease; 44 patients viz 25 males and 19 females belonged to Stage II of Parkinson's Disease; 28 patients viz 18 males and 10 females belonged to Stage III of Parkinson's Disease; 16 patients viz 12 males and 4 females belonged to Stage IV and V of Parkinson's Disease

Overall 118 out of 141 patients (83.7%) of patients had ANS dysfunction. Among 87 males, 72 patients (82.75%) had ANS dysfunction and among 54 females, 46 patients(85.2%) had ANS dysfunction. Singer et al noted that 89% of Parkinsonian patients had at least one of the autonomic symptoms. 80-90 % of PD patients have some ANS symptoms as per Turkka et al (1986)[55].This is consistent with our study where ANS symptoms were present in 83.7% of PD patients.

Among male patients, 22 out of 32(68.75%) belonging to Stage I; 21 out of 25(84%) belonging to Stage II, 17 out of 18(94.4%) belonging to Stage III and all patients(100%) of Stage IV had autonomic dysfunction. Among female patients, 17 out of 21(80.9%) belonging to Stage I ;16 out of 19(84.2%) belonging to Stage II, 9 out of 10(90%) belonging to Stage III and all patients(100%) of Stage IV had autonomic dysfunction. Overall Stage wise 39 patients of 53 patients(73.6%) belonging to Stage I; 37 of 44 (84.1%) belonging to Stage II; 26 of 28 (84.1%) belonging to Stage III and all patients(100%) belonging to Stage IV and V had ANS dysfunction. Hence as the staging of PD increases the prevalence of ANS dysfunction increases both in males and females. Thus ANS dysfunction significantly correlates with staging of PD in both sexes which is similar with studies of Zesiewicz TA et al[51] and Pospíšil P et al[52] in their series.

Among 118 patients, 61male(84.7%) and 21(45.7%) female had sexual dysfunction, 34 males(47.2%) and 36 females(78.3%) had urinary dysfunction, 41 males(56.9%) and 22 females(47.8%) had gastrointestinal tract dysfunction, 27 males(37.5%) and 26 females(56.5%) had cardiovascular dysfunction,37 males(51.3%) and 30 females(65.2%) had thermoregulatory dysfunction. Patients had ANS dysfunction in multiple categories and the percentages observed were within same gender. Among males sexual dysfunction was the most common ANS dysfunction followed by gastrointestinal tract dysfunction, thermoregulatory dysfunction, urinary dysfunction, and cardiovascular dysfunction in that order. Among females urinary dysfunction was the most common followed by thermoregulatory dysfunction and cardiovascular dysfunction. Wüllner U et al[54] in his analysis of Autonomic dysfunction in 3414 Parkinson's disease patients have reported Orthostatic hypotension in 10% of women and 11% of men, urinary incontinence in 22% of women and 21% of men, sexual dysfunction in 8% of women and 30% of men (50% of whom reported erectile dysfunction). According to Singer C et al53, who evaluated autonomic function in forty-eight men with Parkinson's disease (PD), found a higher prevalence of the following symptoms of autonomic dysfunction in the PD patients: erectile dysfunction (60.4 vs. 37.5%), sensation of incomplete bladder emptying (41.6 vs. 15.6%), urgency (45.8

vs. 3.125%), constipation (43.9 vs. 6.25%), dysphagia (22.9 vs. 6.25%) and orthostatic dizziness (21.95 vs. 0%). Sexual dysfunction ranks first similar to our study.

On correlating the age with ANS dysfunction, in 40- 50 group,22(38.6%) did not have ANS dysfunction 28(49.1%) had mild ANS dysfunction 7(12.3%) had moderate ANS dysfunction and none had severe dysfunction. In 50-60 age group, 1 (2.2%) did not have ANS dysfunction, 11(24.4%) had mild ANS dysfunction, 31(68.9%) had moderate ANS dysfunction and 2(4.4%) had severe dysfunction. In 60-70 age group, 5(12.8%) had moderate ANS dysfunction and 34(87.2%) had severe dysfunction. In intial years of the disease, patients did not have ANS dysfunction or only mild to moderate ANS dysfunction only. But as the age advances the severity of dysfunction increases, which is statistically significant (p value<0.0001). There is no significant correlation between males and females reagarding the severity of ANS dysfunction.

On analysing the disease duration with ANS dysfunction, in upto 5 years group,14(25%) did not have ANS dysfunction, 35(62.5%) had mild ANS dysfunction 7(12.5%) had moderate ANS dysfunction and none had severe dysfunction. In 5-7.5 years group, 7 (16.7%) did not have ANS

dysfunction, 4(9.5%) had mild ANS dysfunction, 29(69%) had moderate ANS dysfunction and 2(4.8%) had severe dysfunction. In 7.5-10 years group, 2(8.3%) did not have ANS dysfunction 5(20.8%) had moderate ANS dysfunction and 17(70.8%) had severe dysfunction. In more than 10 years group,2(10.5%) had moderate ANS dysfunction and 17(89.5%) had severe dysfunction. As the disease duration advances the severity of dysfunction increases,with patients in older age group having disease duration more than 10 years have moderate to severe ANS dysfunction and which is statistically significant (p value<0.0001).

On analysing the staging with severity of ANS dysfunction, in Stage I, 14(26.4%) patients did not have ANS dysfunction, 33(62.3%) had mild ANS dysfunction 6(11.3%) had moderate ANS dysfunction and none had severe dysfunction. In Stage II, 7 (15.9%) did not have ANS dysfunction, 6(13.6%) had mild ANS dysfunction, 30(68.2%) had moderate ANS dysfunction and 1(2.3%) had severe dysfunction. In Stage III, 2(7.1%) did not have ANS dysfunction 7(25%) had moderate ANS dysfunction and 19(67.9%) had severe dysfunction. In Stage IV and V, all 16 patients (100%) had severe dysfunction. As the staging advances the severity of dysfunction increases. All patients in Stage IV and V patients had severe ANS dysfunction in all patients which is statistically

significant (p value<0.0001). Pospíšil P and Konečný L et al[52] in their study has concluded that autonomic nervous system dysfunction is more severe in advanced stages of Hoehn and Yahr (stages 2 and 3) than early stages (stage 1) . Hoehn & Yahr (H&Y) stage, disease duration, and age at onset all showed significant correlations with Autonomic dysfunction (Zesiewicz TA et al)[51].

On analysing various sympathetic tests, BP on cold pressor test, BP on isovolumetric exercise, BP on standing, BP on valsalva manouvere, as the stage worsens the abnormality of BP measurements increases and thus they all are significantly correlated with the staging and thus severity. Orthostatic hypotension makes the patients in terminal stages disabled.

Similarly on anlaysing parasympathetic cardiovascular function tests, Heart rate variability ratio(HRV) on standing, HRV on valsalva, HRV on respiration,were abnormal as the staging and disease worsens. Meco et al[22] in his study of Cardiovascular reflexes and autonomic dysfunction in Parkinson's disease analysed in 20 cases heart rate variation during normal respiration,standing and during the Valsalva manoeuvre and blood pressure variation after standing and concluded that significant changes in the different heart rate variation indices were found in the Parkinsonian patients that correlates with both the duration and severity of the

extrapyramidal symptomatology. These results were in consistent with our study. Ludin SM, and Steiger UH et al[45] analysed cardiovascular reflexes in 22 patients and have concluded the heart rate variation evoked by deep breathing as well as the blood pressure response and the heart rate response to sustained isometric exercise were significantly diminished in the patients with idiopathic Parkinson's disease. S.J. Piha' , J.O. Rinne, U.K. Rinne et al [47,48,49] in their study of Autonomic dysfunction in recent onset and advanced Parkinsons's disease, have concluded that in Parkinson's disease a parasympathetic damage occurs which worsens during the course of the disease, and also the orthostatic fall in blood pressure, indicating a sympathetic dysfunction[20]. The dysfunction of cardiovascular autonomic control is thought to correlate with the severity of the disease . (van Dijk *et al.* 1993)[23,24,50,].

Hence prevalence of ANS dysfunction is high in Parkinson disease patients. It correlates well with Age, Duration, Hoehn and Yahr staging. Cardiovascular autonomic function tests also correlate with staging and thus severity of disease. Advancement in management of autonomic symptoms stresses the need for identification of ANS symptoms early so that early treatment gives them good quality of life.

CONCLUSION

CONCLUSIONS

Autonomic nervous system dysfunction in Parkinson's disease is a common problem and it has to be identified early to initiate proper treatment. We conclude the following from our study.

1. The prevalence of ANS dysfunction is significantly high in PD patients of 83.7% . The prevalence is 82.75% in males and 85.2% in females.

2. The prevalence of ANS dysfunction in Males increases as the Hoehn and Yahr stage increases as evidenced by 68.7% of males in stage I and 100% of males in stage IV and V have ANS dysfunction.

3. The prevalence of ANS dysfunction in Females increases as the Hoehn and Yahr stage increases as evidenced by 80.9% of females in stage I and 100% of Females in stage IV and V have ANS dysfunction.

4. Sexual dysfunction(84.7%) is the most common ANS dysfunction in males followed by gastrointestinal(56.9%), and thermoregulatory (51.3%) autonomic disturbances.

5. Urinary disturbances(78.3%), is the most common ANS dysfunction in females followed by thermoregulatory(65.2%),, and cardiovascular disturbances(56.5%).

6. There is a significant correlation between the age and ANS dysfunction. The severity of dysfunction worsens as the age advances, which is statistically significant (p value<0.0001)

7. There is no significant correlation between the sex and severity of ANS dysfunction.

8. As the disease duration advances the severity of dysfunction increases which is statistically significant (p value<0.0001). Patient with disease duration less than 5 years had no or only mild ANS dysfunction, whereas with patients with disease duration more than 10 years had predominantly moderate to severe ANS dysfunction in all patients.

9. There exists a significant correlation between Hoehn and Yahr staging and severity of ANS dysfunction. Patient in stage I had no ANS dysfunction(26.4%) or only mild dysfunction(62.3%) whereas patients in stage IV and V have severe ANS dysfunction (100%).

10. The prevalence of abnormality in Sympathetic cardiovascular autonomic function tests viz BP on cold pressor test, BP on isovolumetric exercise, BP on standing, BP on valsalva manouvere, increases as the stage worsens significantly.

11. The prevalence of abnormality in Parasympathetic cardiovascular autonomic function tests viz Heart rate variability ratio(HRV) on standing, HRV on valsalva, HRV on respiration, also increases as the stage increases.

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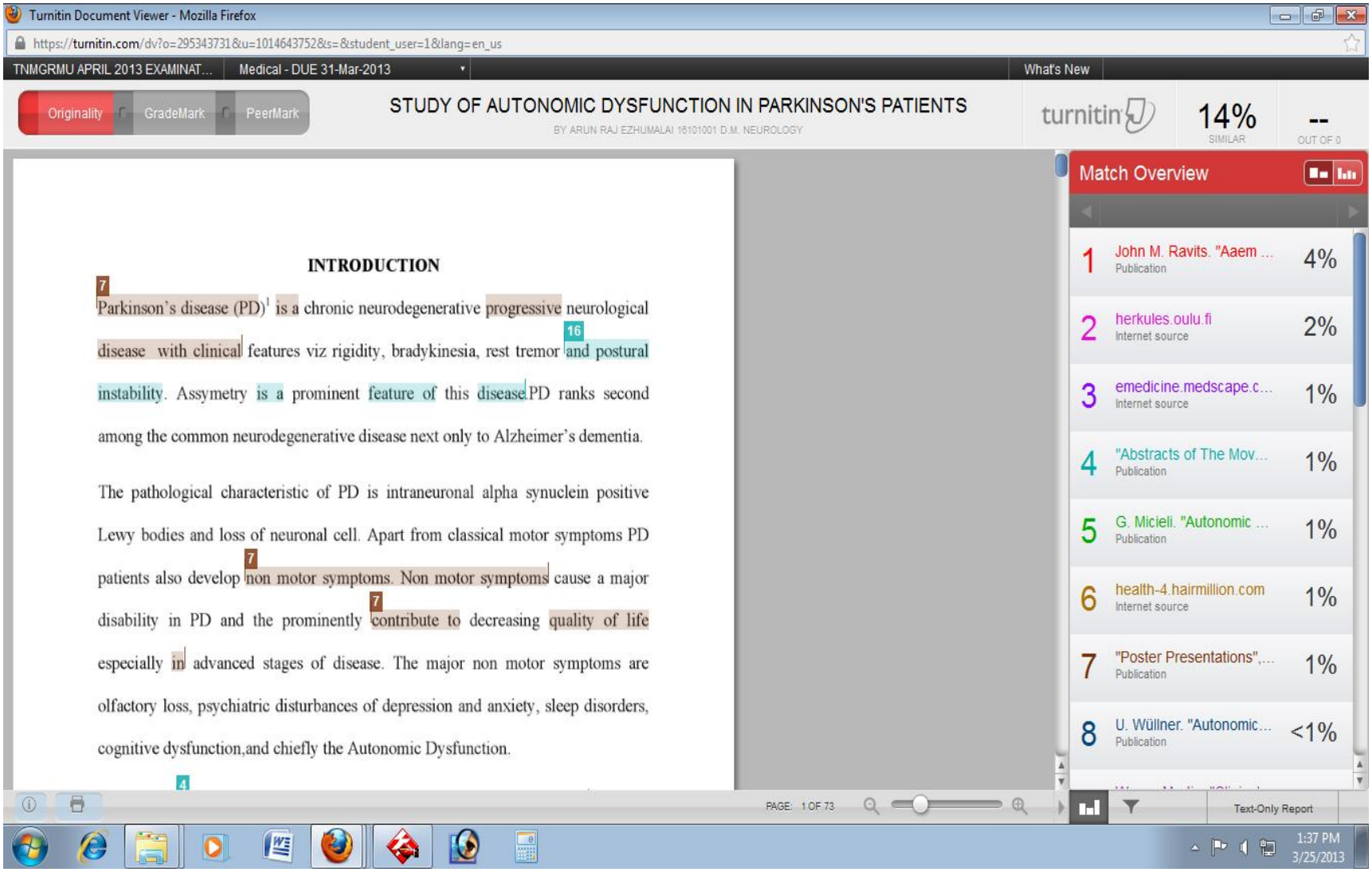
ABBREVIATIONS

Abbreviations

ANS	Autonomic nervous system
HRV	Heart rate variability ratio
BP	Blood pressure
CNS	Central nervous system
ECG	Electrocardiogram
EMG	Electromyogram
HR	Heart rate
MSA	Multiple system atrophy
PD	Parkinson’s disease
RSA	Respiratory sinus arrhythmia
SSR	Sympathetic skin response
QSART	Quantitative sudomotor axon reflex test
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
n	number of patients

ANNEXURES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INTRODUCTION
Parkinson's disease (PD)[1] is a chronic neurodegenerative progressive neurological disease with clinical features viz rigidity, bradykinesia, rest tremor and postural instability. Assymetry is a prominent feature of this disease.PD ranks second among the common neurodegenerative disease next only to Alzheimer's dementia.
The pathological characteristic of PD is intraneuronal alpha synuclein positive Lewy bodies and loss of neuronal cell. Apart from classical motor symptoms PD patients also develop non motor symptoms. Non motor symptoms cause a major disability in PD and the prominently contribute to decreasing quality of life especially in advanced stages of disease. The major non motor symptoms are olfactory loss, psychiatric disturbances of depression and anxiety, sleep disorders, cognitive dysfunction,and chiefly the Autonomic Dysfunction.
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INTRODUCTION Parkinson’s disease (PD)1 is a chronic neurodegenerative progressive neurological disease with clinical features viz rigidity, bradykinesia, rest tremor and postural instability. Assymetry is a prominent feature of this disease.PD ranks second among the common neurodegenerative disease next only to Alzheimer’s dementia. The pathological characteristic of PD is intraneuronal alpha synuclein positive Lewy bodies and loss of neuronal cell. Apart from classical motor symptoms PD patients also develop non motor symptoms. Non motor symptoms cause a major disability in PD and the prominently contribute to decreasing quality of life especially in advanced stages of disease. The major...

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

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CERTIFICATE OF APPROVAL

To
Dr.E. Arunraj
PG in DM Neurology
Madras Medical College, Chennai -3

Dear Dr. E. Arunraj

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Study of autonomic nervous system dysfunction in parkinsonpatients" No.01042012.

The following members of Ethics Committee were present in the meeting held on 19.04.2012 conducted at Madras Medical College, Chennai -3.

1.	Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2.	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	-- Member Secretary
3.	Prof. B. Kalaiselvi MD Prof. of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. of Internal Medicine, MMC, Ch-3	-- Member
5.	Prof. Md. Ali. MD.DM Prof & HOD, Dept. of MGE, MMC, Ch-3	-- Member
6.	Prof.P.Karkuzhali MD Director i/c, Prof., Inst. of Pathology, MMC, Ch-3	-- Member
7.	Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
8.	Prof. A. Radhakrishnan MD Prof of Internal Medicine, MMC, Ch-3	-- Member
9.	Thiru. S. Govindsamy. BABL	-- Lawyer
10.	Tmt. Arnold Soulina MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

PROFORMA

PROFORMA

STUDY OF AUTONOMIC NERVOUS SYSTEM DYSFUNCTION IN PARKINSONISM

Name : **MIN NO :**

Age : **S.NO :**

Sex : **DATE :**

Diagnosis :

Duration of disease :

Symptomatology and duration:

Rigidity :

Tremor :

Postural instability :

Bradykinesia :

Other features

1. :

2. :

3. :

Symmetrical /assymetrical

Treatment history :

Drugs ,dose,duration :

Clinical improvement : static /improved/worsening

General examination:

Systemic examination:

Others:

DM /SHT/OTHER SYSTEMIC DISEASES

SMOKER : YES/NO **ALCOHOLIC: YES/NO**

BLOOD SUGAR

UREA

CREATININE

LIPID PROFILE

CT BRAIN/ MRI BRAIN:

HOEHN AND YAHR STAGING:

AUTONOMIC FUNCTION TESTS

1.Blood Pressure In Supine :

Standing : 1min

3 min

2.Heart Rate Variability Ratio To Standing:

3. Heart Rate Variability Ratio To Deep Breathing:

4. Heart Rate Variability Ratio To Valsalva:

5. Blood Pressure Response To Sustained Handgrip

RestBP Test BP

6. BP Variation To Mental Arithmetic

RestBP Test BP

7. BP Variation To Cold Pressor test

RestBP Test BP

Symptoms

On standing from supine posture

Dizziness /light headedness :

Fainting :

Presyncope or syncope:

Flushing sensation:

Dry skin:

Excessive sweating during day or night:

Dribbling of saliva:

Dysphagia or food struck in mouth:

Feeling of bloatedness:

Constipation:

Invouluntary loss of stools:

Invouluntary loss of urine:

Feeling of incomplete emptying:

Frequency of micturition:

Urgency of micturition:

Nocturia :

Impotence :

Erectile dysfunction:

Ejaculation problem:

Failure to attain orgasm:

ANS Feature	Yes/No	Duration	Onset Related To Disease
Bladder dysfunction			
Bowel dysfunction			
Sexual dysfunction			
Symptoms related to postural hypotension			
Thermoregulatory dysfunction			
Salivation			
Cardiovascular dysfunction			

MASTER CHART

MASTER CHART

M – MALE MOD- MODERATE U – URINARY N – NORMAL

F – FEMALE G- GASTROINTESTINAL S – SEXUAL AN - ABNORMAL

Y – YES C- CARDIAC T – THERMOREGULATORY BP – BLOOD PRESSURE

HRV – HEART RATE VARIABILITY ANS – AUTONOMIC NERVOUS SYSTEM H&Y – HOEHN AND YAHR

SL. NO.	AGE	SEX	ANS DISTURBANCE Y/N	DISEASE DURATION YEARS	TYPE OF ANS DISTURBANCE	TYPE OF ANS DISTURBANCE	STAGING H&Y	SEVERITY OF ANS	BP ON MENTAL ARITHMETIC	BP ON COLD PRESSOR	BP ON POSTURE	BP ON ISOMETRIC EXERCISE	HRV ON STANDING	HRV ON VALSALVA	HRV ON RESPIRATION
1	46	M	Y	4	G		1	mild	N	N	N	N	N	N	N
2	48	M	Y	4.5	G		1	mild	N	N	N	N	N	N	N
3	47	M	Y	4	G		1	mild	N	N	N	N	N	N	N
4	49	M	Y	3.5	S		1	mild	N	N	N	N	N	N	N
5	51	M	Y	3	S		1	mild	N	N	N	N	N	N	N
6	52	M	Y	3.5	S		1	mild	N	N	N	N	N	N	N
7	45	M	Y	3	S		1	mild	N	N	N	N	N	N	N
8	47	M	Y	2.5	S		1	mild	N	N	N	N	N	N	N
9	48	M	Y	4	S		1	mild	N	N	N	N	N	N	N
10	45	M	Y	4.5	S		1	mild	N	N	N	N	N	N	N
11	47	M	Y	4.5	S,T	U	1	mod	N	N	N	N	N	N	N
12	48	M	Y	4	G		1	mild	N	N	N	N	N	N	N
13	51	M	Y	4.5	S		1	mild	N	N	N	N	N	N	N
14	60	M	Y	4	G,S		1	mild	N	N	N	N	N	N	N
15	46	M	Y	3.5	G,S		1	mild	N	N	N	N	N	N	N

SL. NO.	AGE	SEX	ANS DISTURBANCE Y/N	DISEASE DURATION YEARS	TYPE OF ANS DISTURBANCE	TYPE OF ANS DISTURBANCE	STAGING H&Y	SEVERITY OF ANS	BP ON MENTAL ARITHMETIC	BP ON COLD PRESSOR	BP ON POSTURE	BP ON ISOMETRIC EXERCISE	HRV ON STANDING	HRV ON VALSALVA	HRV ON RESPIRATION
16	48	M	Y	3	S		1	mild	N	N	N	N	N	N	N
17	49	M	Y	3.5	G		1	mild	N	N	N	N	N	N	N
18	47	M	Y	3	G		1	mild	N	N	N	N	N	N	N
19	48	M	Y	2.5	S		1	mild	N	N	N	N	N	N	N
20	47	M	Y	4	G		1	mild	N	N	N	N	N	N	N
21	46	M	Y	4.5	S,T	U	1	mod	N	N	N	N	N	N	N
22	48	M	Y	4.5	S,T		1	mild	N	N	N	N	N	N	N
23	53	M	Y	6	G,T	C	2	mod	N	N	N	N	N	AN	N
24	55	M	Y	6.5	G,S,T		2	mod	N	N	N	N	N	N	N
25	56	M	Y	7	G,S,T		2	mod	N	N	N	N	N	N	N
26	53	M	Y	5.5	S,T	C	2	mod	N	N	N	N	AN	N	N
27	54	M	Y	6.5	G,T	U	2	mod	N	N	N	N	N	N	N
28	56	M	Y	7	T	C	2	mild	N	N	N	N	N	N	AN
29	57	M	Y	7.5	S,G,T		2	mod	N	N	N	N	N	N	N
30	54	M	Y	7.5	S	C	2	mild	N	N	N	N	AN	N	N
31	57	M	Y	5	S,T	U	2	mod	N	N	N	N	N	N	N
32	58	M	Y	5	G	U,C	2	mild	N	N	N	N	N	N	AN
33	52	M	Y	6.5	T	U,C	2	mod	N	N	N	N	AN	N	N
34	51	M	Y	6.5	S	U,C	2	mod	N	N	N	N	N	AN	N
35	54	M	Y	5	S,G		2	mild	N	N	N	N	N	N	N
36	54	M	Y	5.5	S,G	C	2	mod	N	N	N	N	AN	N	N

SL. NO.	AGE	SEX	ANS DISTURBANCE Y/N	DISEASE DURATION YEARS	TYPE OF ANS DISTURBANCE	TYPE OF ANS DISTURBANCE	STAGING H&Y	SEVERITY OF ANS	BP ON MENTAL ARITHMETIC	BP ON COLD PRESSOR	BP ON POSTURE	BP ON ISOMETRIC EXERCISE	HRV ON STANDING	HRV ON VALSALVA	HRV ON RESPIRATION
37	52	M	Y	6.5	S,G	C	2	mod	N	N	N	N	N	AN	N
38	58	M	Y	7	T	C,U	2	mod	N	N	N	N	N	N	AN
39	52	M	Y	7.5	S	C,U	2	mod	N	N	N	N	AN	N	N
40	51	M	Y	5.5	S,G	C	2	mod	N	N	N	N	N	N	N
41	58	M	Y	6	S,G	U	2	mod	N	N	N	N	N	N	N
42	52	M	Y	7	S,G	U	2	mod	N	N	N	N	N	N	N
43	51	M	Y	7.5	S,G,T		2	mod	N	N	N	N	N	N	N
44	64	M	Y	8.5	S,G,T	C,U	3	severe	AN	N	AN	N	AN	AN	AN
45	65	M	Y	9	S,G,T	C,U	3	severe	AN	N	AN	N	N	AN	AN
46	64	M	Y	8.5	S,G,T	C,U	3	severe	AN	AN	AN	N	AN	AN	N
47	63	M	Y	9.5	S,G,T	C,U	3	severe	AN	N	AN	N	AN	AN	AN
48	62	M	Y	10.5	S,G	C	3	mod	N	N	N	AN	AN	N	N
49	64	M	Y	9.5	S,G,T	C,U	3	severe	AN	AN	AN	N	AN	AN	N
50	65	M	Y	10	S,G,T		3	mod	N	N	N	N	N	N	N
51	64	M	Y	9.5	S,G,T	C,U	3	severe	N	N	AN	AN	AN	AN	AN
52	63	M	Y	10	S,G	C,U	3	mod	N	N	N	N	AN	N	AN
53	62	M	Y	10.5	S,G,T	C,U	3	severe	AN	N	AN	N	N	AN	AN
54	59	M	Y	10.5	S,G	C	3	mod	N	AN	N	N	AN	N	N
55	64	M	Y	11	S,G,T	C,U	3	severe	N	AN	AN	N	AN	AN	AN
56	68	M	Y	11.5	S,G	C,U	3	severe	AN	N	AN	AN	AN	AN	AN
57	69	M	Y	10.5	S,G	C,U	3	severe	AN	AN	N	AN	AN	AN	N

SL. NO.	AGE	SEX	ANS DISTURBANCE Y/N	DISEASE DURATION YEARS	TYPE OF ANS DISTURBANCE	TYPE OF ANS DISTURBANCE	STAGING H&Y	SEVERITY OF ANS	BP ON MENTAL ARITHMETIC	BP ON COLD PRESSOR	BP ON POSTURE	BP ON ISOMETRIC EXERCISE	HRV ON STANDING	HRV ON VALSALVA	HRV ON RESPIRATION
58	70	M	Y	9.5	S,G	C,U	3	severe	AN	AN	AN	N	AN	AN	AN
59	63	M	Y	10.5	S,G	C,U	3	severe	N	AN	AN	AN	AN	AN	AN
60	64	M	Y	10	S,G,T	C,U	3	severe	AN	N	AN	AN	AN	AN	AN
61	61	M	Y	10	S,G,T	C,U	4	severe	AN	AN	N	AN	AN	AN	AN
62	65	M	Y	10.5	S,G,T	C,U	4	severe	AN	AN	AN	N	AN	AN	AN
63	62	M	Y	14	S,G,T	C	4	severe	AN	AN	AN	AN	AN	AN	AN
64	63	M	Y	12	S,G,T	C,U	4	severe	AN	AN	AN	AN	N	AN	AN
65	61	M	Y	12	S,G,T	C,U	4	severe	AN	AN	AN	AN	AN	AN	AN
66	68	M	Y	12.5	S,G,T	C,U	4	severe	AN	AN	AN	AN	AN	AN	N
67	64	M	Y	10.5	S,G,T	C,U	4	severe	AN	AN	AN	AN	AN	AN	AN
68	63	M	Y	10.5	S,G,T	C,U	4	severe	AN	AN	AN	AN	AN	AN	AN
69	63	M	Y	11	S,G,T	C,U	4	severe	AN	AN	AN	AN	AN	AN	AN
70	66	M	Y	12	S,G,T	C,U	4	severe	AN	AN	AN	AN	AN	AN	AN
71	67	M	Y	10.5	S,G,T	C,U	4	severe	AN	AN	AN	AN	AN	AN	AN
72	63	M	Y	12	S,G,T	C,U	4	severe	AN	AN	AN	AN	AN	AN	AN
73	43	M	No	4	---	---	1	NIL	N	N	N	N	N	N	N
74	42	M	No	4.5	---	---	1	NIL	N	N	N	N	N	N	N
75	41	M	No	4	---	---	1	NIL	N	N	N	N	N	N	N
76	40	M	No	3.5	---	---	1	NIL	N	N	N	N	N	N	N
77	48	M	No	3	---	---	1	NIL	N	N	N	N	N	N	N

SL. NO.	AGE	SEX	ANS DISTURBANCE Y/N	DISEASE DURATION YEARS	TYPE OF ANS DISTURBANCE	TYPE OF ANS DISTURBANCE	STAGING H&Y	SEVERITY OF ANS	BP ON MENTAL ARITHMETIC	BP ON COLD PRESSOR	BP ON POSTURE	BP ON ISOMETRIC EXERCISE	HRV ON STANDING	HRV ON VALSALVA	HRV ON RESPIRATION
78	45	M	No	3.5	---	---	1	NIL	N	N	N	N	N	N	N
79	43	M	No	3	---	---	1	NIL	N	N	N	N	N	N	N
80	42	M	No	2.5	---	---	1	NIL	N	N	N	N	N	N	N
81	43	M	No	4	---	---	1	NIL	N	N	N	N	N	N	N
82	42	M	No	5	---	---	1	NIL	N	N	N	N	N	N	N
83	46	M	No	6.5	---	---	2	NIL	N	N	N	N	N	N	N
84	47	M	No	7	---	---	2	NIL	N	N	N	N	N	N	N
85	43	M	No	5.5	---	---	2	NIL	N	N	N	N	N	N	N
86	42	M	No	6	---	---	2	NIL	N	N	N	N	N	N	N
87	41	M	No	9	---	---	3	NIL	N	N	N	N	N	N	N
88	48	F	Y	4	T		1	mild	N	N	N	N	N	N	N
89	49	F	Y	4.5	T		1	mild	N	N	N	N	N	N	N
90	46	F	Y	4	T	U	1	mild	N	N	N	N	N	N	N
91	47	F	Y	4	T	U	1	mild	N	N	N	N	N	N	N
92	40	F	Y	4.5	T	U	1	mild	N	N	N	N	N	N	N
93	48	F	Y	4	T	U	1	mild	N	N	N	N	N	N	N
94	45	F	Y	3.5	T	U	1	mild	N	N	N	N	N	N	N
95	43	F	Y	3	T	U	1	mild	N	N	N	N	N	N	N
96	42	F	Y	3.5	T	U	1	mild	N	N	N	N	N	N	N
97	43	F	Y	3	S,T	U	1	mod	N	N	N	N	N	N	N
98	42	F	Y	3.5	T	U	1	mild	N	N	N	N	N	N	N

SL. NO.	AGE	SEX	ANS DISTURBANCE Y/N	DISEASE DURATION YEARS	TYPE OF ANS DISTURBANCE	TYPE OF ANS DISTURBANCE	STAGING H&Y	SEVERITY OF ANS	BP ON MENTAL ARITHMETIC	BP ON COLD PRESSOR	BP ON POSTURE	BP ON ISOMETRIC EXERCISE	HRV ON STANDING	HRV ON VALSALVA	HRV ON RESPIRATION
99	46	F	Y	4	T	U	1	mild	N	N	N	N	N	N	N
100	47	F	Y	4.5	S,G,T		1	mod	N	N	N	N	N	N	N
101	48	F	Y	4	T	U	1	mild	N	N	N	N	N	N	N
102	53	F	Y	3.5	S,G,T		1	mod	N	N	N	N	N	N	N
103	52	F	Y	3	S,G,T		1	mod	N	N	N	N	N	N	N
104	54	F	Y	3.5	T	U	1	mild	N	N	N	N	N	N	N
105	56	F	Y	6.5	S,G,T		2	mod	N	N	N	N	N	N	N
106	57	F	Y	7	G,T	U	2	mod	N	N	N	N	N	N	N
107	54	F	Y	6.5	S,G,T		2	mod	N	N	N	N	N	N	N
108	53	F	Y	6.5	T	C,U	2	mod	N	N	AN	N	N	N	AN
109	59	F	Y	7	T	C,U	2	mod	N	N	N	N	N	N	N
110	53	F	Y	5.5	G,T	U	2	mod	N	N	N	N	N	N	N
111	54	F	Y	6.5	G,T	U	2	mod	AN	N	N	N	N	N	N
112	55	F	Y	7	G,T	C,U	2	mod	N	N	N	N	AN	N	N
113	52	F	Y	6.5	G,T	C	2	mod	N	N	N	N	N	N	N
114	49	F	Y	7	G	C,U	2	mod	N	N	N	N	N	N	AN
115	51	F	Y	5.5	S	U	2	mild	N	AN	N	N	N	N	N
116	45	F	Y	6.5	S,G	C	2	mod	N	N	N	AN	N	AN	N
117	48	F	Y	7	S,T	C	2	mod	N	N	N	N	AN	N	N
118	54	F	Y	5.5	G	C	2	mild	N	AN	AN	N	N	N	N
119	58	F	Y	6	S,G	C,U	2	severe	AN	N	N	N	AN	AN	AN

SL. NO.	AGE	SEX	ANS DISTURBANCE Y/N	DISEASE DURATION YEARS	TYPE OF ANS DISTURBANCE	TYPE OF ANS DISTURBANCE	STAGING H&Y	SEVERITY OF ANS	BP ON MENTAL ARITHMETIC	BP ON COLD PRESSOR	BP ON POSTURE	BP ON ISOMETRIC EXERCISE	HRV ON STANDING	HRV ON VALSALVA	HRV ON RESPIRATION
120	56	F	Y	6	G	C,U	2	mod	N	AN	N	AN	N	N	N
121	59	F	Y	8	S,G	C,U	3	severe	AN	AN	N	AN	AN	AN	AN
122	58	F	Y	8.5	G	C,U	3	mod	N	AN	N	N	N	N	AN
123	61	F	Y	9	S,G	C,U	3	severe	AN	AN	AN	AN	AN	AN	AN
124	62	F	Y	9.5	S,G	C,U	3	severe	AN	AN	AN	AN	AN	AN	AN
125	64	F	Y	7.5	S,G	C,U	3	severe	AN	AN	AN	AN	AN	AN	AN
126	70	F	Y	8	S,G	C,U	3	severe	AN	AN	N	AN	AN	AN	AN
127	63	F	Y	8.5	G	C,U	3	mod	N	AN	AN	AN	N	AN	AN
128	65	F	Y	8	S,G	C,U	3	severe	AN	AN	AN	AN	AN	AN	AN
129	64	F	Y	8.5	T	C,U	3	mod	AN	AN	AN	AN	N	AN	AN
130	63	F	Y	9	G,T	C,U	4	severe	AN	AN	AN	N	AN	AN	AN
131	63	F	Y	9.5	G,T	C,U	4	severe	AN	AN	AN	AN	AN	AN	AN
132	68	F	Y	10	S,G,T	C,U	4	severe	AN	AN	AN	AN	AN	AN	AN
133	65	F	Y	10.5	S,G	C,U	4	severe	AN	AN	AN	N	AN	AN	AN
134	46	F	No	4.5	---	---	1	NIL	N	N	N	N	N	N	N
135	45	F	No	4	---	---	1	NIL	N	N	N	N	N	N	N
136	43	F	No	4.5	---	---	1	NIL	N	N	N	N	N	N	N
137	54	F	No	3.5	---	---	1	NIL	N	N	N	N	N	N	N
138	50	F	No	6.5	---	---	2	NIL	N	N	N	N	N	N	N
139	46	F	No	7.5	---	---	2	NIL	N	N	N	N	N	N	N
140	42	F	No	6	---	---	2	NIL	N	N	N	N	N	N	N
141	45	F	No	8.5	---	---	3	NIL	N	N	N	N	N	N	N